PROTOCOL

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER (MORPHEUS-LUNG)**
PROTOCOL NUMBER:	BO39610
VERSION NUMBER:	17
EUDRACT NUMBER:	2017-001267-21
IND NUMBER:	134,543
NCT NUMBER:	NCT03337698
TEST PRODUCTS:	Atezolizumab (RO5541267), Cobimetinib (RO5514041), Evolocumab, Ipatasertib (RO5532961), Linagliptin, Docetaxel, Sacituzumab Govitecan, and Bevacizumab (RO4876646)
MEDICAL MONITOR:	Jan Pintoffl, M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Mar-2022 02:50:41	Company Signatory	Cha, Edward (chae1)

CONFIDENTIAL

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PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
17	*See electronic date stanp on title page*	—	—	—
13	*23 March 2021*	—	—	—
10	25 August 2020	*France*	*16*	*15 July 2021*
		Spain	*15*	*12 April 2021*
		France	*14*	*6 May 2021*
7	10 January 2020	Spain	12	22 December 2020
		France	11	10 September 2020
4	2 May 2019	France	9	2 April 2020
		France	8	8 January 2020
3	25 October 2018	France	6	12 August 2019
		France	5	14 May 2019
1	14 July 2017	VHP	2	8 November 2017

PROTOCOL AMENDMENT, VERSION 17: RATIONALE

Protocol BO39610 has primarily been amended to remove an experimental arm. Additionally, risks and management guidelines for atezolizumab have been updated to align with the latest Atezolizumab Investigator's Brochure (Version 18). Changes to the protocol, along with a rationale for each change, are summarized below:

- The treatment arm atezolizumab plus CPI-444 (Atezo + CPI-444) have been removed (Sections 1.3, 3.1.1, 3.1.2, 3.1.3, 4.1.2; 4.3.1, 5.3.5.12, 5.7; Section 4.1.2.6 has been deleted and subsequent sections renumbered); Appendix 13 has been removed.
- The enrollment status of the atezolizumab plus docetaxel treatment arm in Stage 1 and Stage 2 have been updated to "closed and not enrolling" and "not enrolling", respectively (Sections 3.1.1 and 3.1.3).
- Benefit–risk assessment and guidance on concomitant administration of COVID-19 vaccines has been added (Section 1.4, Appendices A7–4.2.1, A8–4.2.1, A9–4.2.1, A11–4.2.1, A12–4.2.1, A14–4.2.1, A15–4.2.1, A16–4.2.1, A17–4.2.1, A18–4.2.1, and A19–4.2.1).
- The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix (former Appendix 2) has been removed as the Sponsor no longer plans to perform these analyses (Sections 2, 3.1.4, 4.5.5, 6.4.3; Section 3.3.3 has been deleted and subsequent sections have been renumbered). Old Appendix 20 Schedule of Activities for Screening has moved to Appendix 2 as a result.
- Text has been added to clarify that, if tumor assessment scans for an experimental arm are submitted for evaluation by an independent review facility, scans for the corresponding control arm will also be submitted (Section 3.1.4).
- The responsibilities of the Investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 3.1.4, 4.1.1.1, 4.1.1.3, 4.1.2.2, 4.1.2.8, 4.5.8, Appendices 2, 4, 6, A7–4.1.2, A7–4.2.2.1, A7–5.1.2.2, A7–5.1.2.3, A7–6, A8–4.1.2.1, A8–4.1.2.2, A8–4.2.2.1, A8–4.2.2.2, A8–5.1.4.2, A8–5.1.4.3, A8–6, A9–4.1.2.1, A9–4.1.2.2, A9–4.2.2.1, A9–5.1.4.2, A9–5.1.4.3, A9–6, A10–1.1.2, A10–2.1.2.3, A10–3, A11–4.1.2, A11–4.2.1, A11–4.2.2.1, A11–4.2.2.2, A11–4.2.2.3, A11–5.1.4.2, A11–5.1.4.3, A11–6, A12–4.1.2.1, A12–4.1.2.2, A12–5.1.4.2, A12–5.1.4.3, A12–6, A14–4.1.2.1, A14–4.1.2.2, A14–4.2.2.1, A14–5.1.5.2, A14–5.1.5.3, A14–6, A15–4.1.2.1, A15–4.1.2.2, A15–4.2.2.1, A15–5.1.5.2, A15–5.1.5.3, A15–6, A16–4.1.2.1, A16–4.1.2.2, A16–4.2.2.1, A16–5.1.4.2, A16–5.1.4.3, A16–6, A17–4.1.2.1, A17–4.1.2.2, A17–4.2.2.1, A17–5.1.4.2, A17–5.1.4.3, A17–6, A18–4.1.2.1, A18–4.1.2.2, A18–4.2.2.1, A18–5.1.4.2, A18–5.1.4.3, A18–6, and A19–4.1.2.1, A19–4.1.2.2, A19–4.2.2.1, A19–5.1.6.2, A19–5.1.6.3, and A19–6).
- Text has been added to clarify the duration of long-term follow-up data collection for patients on a specific treatment arm (Section 4.6.1, Appendices A8–6, A9–6, A11–6, A12–6, A14–6, A15–6, A16–6, A17–6, A18–6, and A19–6).

- The procedures for reporting infusion-related reactions (IRRs) have been modified to include reporting of cytokine-release syndrome (CRS), as there may be significant overlap in signs and symptoms of IRRs and CRS (Section 5.3.5.1).
- Text has been revised to note that 95% confidence intervals will be calculated using normal approximation of the binomial distribution (Sections 6.4.1 and 6.4.2).
- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in MedDRA (Appendix 4).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 18 (Appendices 6, A8-5.4.1.3, A11-5.4.1.3, A18-5.4.1.3, and A19-5.1.6.3).
- The Screening Schedule of Activities has been moved to precede the first treatment arm appendix in the protocol to align with the sequence of activities for patients who enroll in the study (old Appendix 20 moved to new Appendix 2).
- An additional footnote has been added to note assessments that may be performed within 24 hours prior to dosing during the treatment period (Appendices A7–6, A8–6, A9–6, A10–6, A11–6, A12–6, A14–6, A15–6, A16–6, A17–6, A18–6, and A19–6).
- Safety and adverse event management guidelines have been updated to include CRS (Appendices A8–5.1.3, A11–5.1.4.3, A12–5.1.4.3, A18–5.1.4.3, and A19–5.1.6.3).
- The list of risks associated with ipatasertib and the adverse event management guidelines have been updated in the atezolizumab plus ipatasertib arm to align with the Ipatasertib Investigator’s Brochure, Version 13 (Appendices A11-5.1.2 and A11-5.1.4.3).
- Management guidelines for IRRs, gastrointestinal toxicity, and neutropenia in the atezolizumab plus sacituzumab govitecan arm have been clarified (Appendix A12-5.1.4.3).
- To provide additional flexibility for patients and study sites, it has been clarified that the 96-hour window for laboratory testing is prior to dosing during the treatment period (Appendices A18–6 and A19–6).
- Text from Section 4.2 providing guidelines for patients randomized to the atezolizumab plus bevacizumab and radiotherapy treatment arm but are unable to start radiotherapy due to clinical or technical reasons, has been added to Appendix A19-4.1.3 for clarity.

Additional minor changes have been made to improve clarity and consistency.
New information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER (MORPHEUS-LUNG)**
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MEDICAL MONITOR:	Jan Pintoffl, M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by Covance.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH METASTATIC NON–SMALL CELL LUNG CANCER (MORPHEUS-LUNG)**
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PHASE:	Ib/II
INDICATION:	NSCLC
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic non–small cell lung cancer (NSCLC). Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 1) and Stage 2 (see Table 2).

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause • OS at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 1 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 2 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥ 4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥ 12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each (as appropriate) drug at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

Table 2 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoints
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1.

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with metastatic NSCLC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients with high tumor programmed death ligand 1 (PD-L1) expression (tumor proportion score [TPS] $\geq$ 50%, as determined through use of the Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay) who have received no prior systemic therapy for metastatic NSCLC, and Cohort 2 will consist of patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/programmed cell death protein 1 (PD-1) checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression. In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Table 3). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2; see Table 4).

Because the treatment landscape for first-line metastatic NSCLC has evolved since the initiation of this study, with new and highly effective treatment options being available in this setting, patient enrollment into Cohort 1 has been suspended as of November 2018, and patients will no longer be enrolled into Cohort 1. Patients already enrolled in Cohort 1 will continue to be treated and monitored per protocol and may be eligible for Stage 2 treatment.

Stage 1

During Stage 1, patients in Cohort 1 will be randomly assigned to a control arm (atezolizumab [Atezo]) or an experimental arm consisting of atezolizumab in combination with cobimetinib (Atezo + Cobi) and patients in Cohort 2 will be randomly assigned to a control arm (docetaxel) or an experimental arm consisting of atezolizumab in combination with cobimetinib (Atezo + Cobi), ipatasertib (Atezo + Ipat), bevacizumab (Atezo + Bev), bevacizumab and radiotherapy (Atezo + Bev + RTx), docetaxel (Atezo + Docetaxel), sacituzumab govitecan (Atezo + SG), or evolocumab (Atezo + Evo).

Approximately 255–435 patients will be enrolled during Stage 1. Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase. Approximately 40 patients will be enrolled in the ipatasertib-containing arm during the preliminary phase to ensure a sufficient number of patients with PI3K/Akt pathway alterations, and 40 patients will be enrolled in the bevacizumab-containing arms during the preliminary phase to ensure a sufficient number of patients with STK11/LKB1 mutations. Thirty patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low trophoblast cell-surface antigen 2 (TROP-2) expression. Twenty patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high proprotein convertase subtilisin/kexin type 9 (PCSK9) expression (PCSK9-high) and low PCSK9 expression (PCSK-low). Additional patients may be enrolled in the Atez + Evo arm to ensure that at least 10 patients with high PCSK9 expression are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase. Fifteen patients will be enrolled in all other experimental arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase. Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the mandatory serial biopsy arms, and the randomization ratio will depend on the number of experimental arms that

are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see criteria below).

Table 3 Stage 1 Treatment Regimens

Cohort (Enrollment Status)	Study Treatment	No. of Patients [a]	
		Preliminary Phase	Expansion Phase [b, c]
1 (not enrolling [d, e])	Atezo	Variable [a]	
	Atezo + Cobi [f]	15	25
2 (enrolling [d])	Docetaxel	Variable [a]	
	Atezo + Cobi [f]	15	25
	Atezo + Evo	20 [g]	25
	Atezo + Ipat	40	25
	Atezo + Docetaxel [f]	15	25
	Atezo + Bev	40	25
	Atezo + Bev + RTx	40	25
	Atezo + SG	30 [h]	25

Atezo = atezolizumab; Bev = bevacizumab; CEA = carcinoembryonic antigen; Cobi = cobimetinib; Evo = evolocumab; Ipat = ipatasertib; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTx = radiotherapy; SG = sacituzumab govitecan; TROP-2 = trophoblast cell-surface antigen 2.

[a] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 35% of patients will be randomly allocated to a control arm.

[b] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase.

[c] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase.

[d] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

[e] Further enrollment in Cohort 1 has been suspended as of November 2018.

[f] This arm is closed and will be removed when the last patient discontinues from the study.

[g] Approximately 20 patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high PCSK9 expression (PCSK9-high) and low PCSK9 expression (PCSK9-low) to facilitate the evaluation of benefit and risk in these subpopulations. Additional patients may be enrolled in the Atezo + Evo arm to ensure that at least 10 patients with high PCSK9 expression are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase.

[h] 30 patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low TROP-2 expression to facilitate the evaluation of the benefit risk of these subpopulations.

Patients in the docetaxel control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Patients in the atezolizumab control arm and the atezolizumab combination arms will be treated until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Patients in the atezolizumab plus docetaxel arm will continue to receive docetaxel

until unacceptable toxicity or disease progression per RECIST v1.1; atezolizumab can be continued until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease. Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with cancer immunotherapies (CITs) (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Mandatory Serial Biopsy Arms at Participating Sites

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial biopsy arm at the time that arm is open for expansion. This arm will consist of patients at participating sites who are willing to undergo an on-treatment biopsy.

Enrollment in a mandatory serial biopsy arm is contingent upon the review and approval of mandatory serial biopsies by each site's Institutional Review Board or Ethics Committee and, if applicable, an appropriate regulatory body. If a site has not been granted approval for mandatory serial biopsies, this section of the protocol will not be applicable at that site.
The objective of the mandatory serial biopsy arms is to analyze serial tissue samples (including pre-treatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Biomarkers may include those that inform stromal and immune biology.

Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory biopsy arm is open within Cohort 1 or Cohort 2, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination within each cohort.

Patients enrolled in a mandatory biopsy arm will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy at Week 4 ($\pm$1 week) after initiation of CIT combination treatment (if deemed clinically feasible by the investigator).

To be eligible for a mandatory serial biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies $\geq$1 cm apart.

Patients enrolled in a mandatory serial biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

Stage 2

During Stage 1, patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (as described above), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2, as outlined in Table 4, provided they meet the eligibility criteria and a Stage 2 arm is open for enrollment.

Assignment to Stage 2 treatment arms will be determined by histologic type (non-squamous vs. squamous) for patients in Cohort 1 but not for patients in Cohort 2, as shown in Table 4. Patients in Cohort 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (docetaxel control arm), loss of clinical benefit (atezolizumab control arm and atezolizumab combination arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 4 Stage 2 Treatment Regimens

Cohort (Enrollment Status)	Histologic Type	Study Treatment
1 (not enrolling [a])	Non-squamous	Atezo + Pem + Carbo
	Squamous	Atezo + Gem + Carbo
2 (*not* enrolling [a])	Non-squamous or squamous	Atezo + Docetaxel [b]
2 (enrolling [a])		Atezo + Lina

Atezo = atezolizumab; Carbo = carboplatin; Gem = gemcitabine;
Lina = linagliptin; Pem = pemetrexed.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

[b] Patients who are enrolled in the Docetaxel control arm and the Atezo + Docetaxel arm in Stage 1 are not eligible to receive this study treatment in Stage 2.

The Sponsor may decide to discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Patients will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 48 weeks and then every 6 or 12 weeks thereafter. Response will be assessed by the investigator using RECIST v1.1. If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm *and the corresponding control arm* be submitted for evaluation by an independent review facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue *may* be discussed with the Medical Monitor. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (docetaxel control arm), or loss of clinical benefit as determined by the investigator (atezolizumab control arm and experimental arms) (if deemed clinically feasible by the investigator). Blood samples will be collected at screening and treatment discontinuation for blood-based next-generation sequencing (NGS) circulating tumor DNA (ctDNA) testing. For patients enrolled in a mandatory serial biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research.

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

NUMBER OF PATIENTS

Approximately 255–435 patients will be enrolled in the study.

TARGET POPULATION

INCLUSION CRITERIA

Patients must meet all of the criteria outlined in Sections 1 and 2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 2 and 3 to qualify for Stage 2.

Section 1: Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥ 18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1
- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically or cytologically confirmed metastatic, non-squamous or squamous NSCLC

  Histologic classification may be based on tumor specimens collected prior to metastasis. Patients with tumors of mixed histology must be classified as non-squamous or squamous on the basis of the major histological component.
- For patients in Cohort 1: no prior systemic therapy for metastatic NSCLC

  Patients who received chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease in the neoadjuvant or adjuvant setting are eligible for the study if therapy was completed at least 6 months prior to initiation of study treatment.
- For patients in Cohort 2: disease progression during or following treatment for metastatic or locally advanced, inoperable NSCLC that consisted of a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy (in either order), for a maximum of two prior lines of systemic therapy

  Patients with disease progression or recurrence within ≤ 6 months after completion of their definitive therapy for locally advanced disease may be allowed to participate in Cohort 2, provided their treatment for locally advanced inoperable NSCLC included a combination of at least a platinum-based chemotherapy (e.g., cisplatin or carboplatin) and PD-L1/PD-1 checkpoint inhibitor.

  Prior exposure to anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies is allowed if used in combination with a PD-L1/PD-1 checkpoint inhibitor.
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue requires discussion with the Medical Monitor.

  A formalin-fixed, paraffin-embedded tumor specimen in a paraffin block (preferred) or at least 15-16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report to the designated central laboratory, once the patient is randomized.
- Availability of peripheral blood for NGS ctDNA testing

- For patients in Cohort 1: High tumor PD-L1 expression, defined as TPS $\geq 50\%$, as determined by a local laboratory through use of a protocol-specified assay, as described below:
  - U.S. sites: FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay
  - Ex-U.S. sites: health authority–approved or CE-marked assay consisting of either the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay

Section 2: Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

    Patients may be transfused to meet this criterion.
  - For patients in Cohort 1: AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN) with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - For patients in Cohort 2: liver function test results that meet <u>one</u> of the following sets of criteria:

    a) AST, ALT, and ALP $\leq 2.5 \times$ ULN

    b) AST and ALT $\leq 1.5 \times$ ULN and ALP $\leq 5 \times$ ULN
  - For patients in Cohort 1: bilirubin $\leq 1.5 \times$ ULN, with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - For patients in Cohort 2: bilirubin $\leq 1.0 \times$ ULN, with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- Tumor accessible for biopsy
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as outlined for each specific treatment arm
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm

Section 3: Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0–2
- Patients in the atezolizumab control arm: ability to initiate Stage 2 treatment within 3 months after experiencing loss of clinical benefit as determined by the investigator while receiving Stage 1 treatment
- Patients in the docetaxel control arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity, or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Patients in an atezolizumab-containing experimental arm during Stage 1 with the exception of the atezolizumab plus docetaxel arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator while receiving Stage 1 treatment
- Patients in the atezolizumab plus docetaxel arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity related to docetaxel or loss of clinical benefit as determined by the investigator or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator)

EXCLUSION CRITERIA

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 5. If a patient is eligible only for a control arm, the patient will not be enrolled in the study. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 5 Arm-Specific Exclusion Criteria

Stage	Cohort	Treatment Arm	Applicable Exclusion Criteria
1	1	Atezo	Sections 1 and 2
		Atezo + Cobi	Sections 1, 2, and 3
	2	Docetaxel	Sections 1, 2, and 4
		Atezo + Cobi	Sections 1, 2, 3, and 4
		Atezo + Ipat	Sections 1, 2, 4, and 5
		Atezo + Evo	Sections 1 and 2
		Atezo + Docetaxel	Sections 1, 2, and 4
		Atezo + Bev	Sections 1, 2, 4, and 6
		Atezo + Bev + RTx	Sections 1, 2, 7, and 7
		Atezo + SG	Sections 1 and 2
2	1	Atezo + Pem + Carbo	Sections 2 and 8
		Atezo + Gem + Carbo	Sections 2 and 9
	2	Atezo + Docetaxel	Sections 2 and 4
		Atezo + Lina	Sections 2 and 10

Atezo = atezolizumab; Bev = bevacizumab; Carbo = carboplatin; Cobi = cobimetinib; Evo = evolocumab; Gem = gemcitabine; Ipat = ipatasertib; Lina = linagliptin; Pem = pemetrexed; RTx = radiotherapy; SG = sacituzumab govitecan.

Section 1: Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- Activating mutation in the *EGFR* gene or *ALK* gene rearrangement

  Patients with unknown *EGFR* and/or *ALK* status will undergo testing at a local laboratory at screening with the exception of patients with squamous NSCLC.
- Prior treatment with any of the protocol-specified study treatments (including TROP-2-targeting agents), with the following exception:

  Patients in Cohort 2 who received atezolizumab, bevacizumab, pemetrexed, gemcitabine, and/or carboplatin for treatment of NSCLC as well as patients who received evolocumab for an approved indication are eligible for the study.
- Prior treatment with a topoisomerase 1 inhibitor
- For patients in Cohort 2: prior treatment with a T-cell co-stimulating therapy or an immune checkpoint inhibitor other than a PD-L1/PD-1 checkpoint inhibitor and anti–CTLA-4 antibodies

  Patients who discontinued a PD-L1/PD-1 checkpoint inhibitor primarily for toxicity or intolerability are not eligible for the study.
- For patients in Cohort 2: immune checkpoint inhibitor or biologic treatment (e.g., bevacizumab) within 2 weeks prior to initiation of study treatment, or other systemic treatment for NSCLC within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Eligibility only for the control arm

Section 2: Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor–α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected serum calcium $>$ ULN)
- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of CNS metastases treated with CNS-directed therapies (e.g., stereotactic body radiotherapy [SBRT], whole brain radiotherapy [WBRT]) are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.
  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  – There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
  – The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or WBRT within 14 days prior to initiation of study treatment.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $< 10\%$ of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- History of malignancy other than NSCLC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival [OS] rate $> 90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤ 1 or better, with the exception of alopecia of any grade, Grade ≤ 2 peripheral neuropathy, and immune checkpoint inhibitor-related hypothyroidism Grade ≤ 2

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

Section 3: Additional Exclusion Criteria for Atezo + Cobi Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo + Cobi arm during Stage 1:

- Prior treatment with mitogen-activated protein kinase (MAPK) inhibitors (including cobimetinib)
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Left ventricular ejection fraction below institutional lower limit of normal or below 50%, whichever is lower
- Known risk factors for ocular toxicity, consisting of any of the following:
  - History of serous retinopathy
  - History of retinal vein occlusion (RVO)
  - Evidence of ongoing serous retinopathy or RVO at baseline

Section 4: Additional Exclusion Criteria for Docetaxel-Containing Arms during Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from docetaxel-containing arms during Stage 2:

- Prior treatment with docetaxel
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade ≥ 2 peripheral neuropathy
- Treatment with strong inhibitors or strong inducers of CYP3A4 within 14 days prior to initiation of study treatment or anticipation of need for such treatment during study treatment

Section 5: Additional Exclusion Criteria for Atezo + Ipat Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the ipatasertib-containing arm during Stage 1:

- Prior treatment with ipatasertib or other Akt inhibitors
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceremia
- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication are allowed.

Diabetic patients with fasting total serum glucose > 8.3 mmol/L (150 mg/dL) and/or HbA1C > 7.5 are not eligible for enrollment.

- Congenital long QT syndrome or screening QT interval corrected through use of Fridericia's formula > 480 ms
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, evidence of prior myocardial infarction
- Treatment with strong CYP3A4 inducers or inhibitors within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug, or anticipation of the need for such treatment while on study

Section 6: Additional Exclusion Criteria for Bevacizumab-Containing Arms during Stage 1

Patients who meet any of the following criteria will be excluded from the bevacizumab-containing arms during Stage 1:

- Patients with squamous NSCLC
- Inadequately controlled hypertension (defined as systolic blood pressure [BP] > 150 mmHg and/or diastolic BP > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions

  Anti-hypertensive therapy to achieve these parameters is allowed.
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (≤ 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day)

  Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed. However, the use of direct oral anticoagulant therapies, such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®), is not recommended due to bleeding risk.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to initiation of study treatment
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, within 6 months prior to initiation of study treatment or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment

  Patients with signs or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Grade ≥ 2 proteinuria, as demonstrated by ≥2+ protein on dipstick urinalysis and ≥ 1.0 g of protein in a 24-hour urine collection

All patients with ≥ 2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with < 2+ protein on dipstick urinalysis are eligible for the study.

- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (< 30 mm from the carina) of large volume
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Ablative radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure

Section 7: Additional Exclusion Criteria for Radiotherapy-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the radiotherapy-containing arm during Stage 1:

- Patients who meet any of the exclusion criteria for bevacizumab-containing arms
- Lack of lesions where SBRT can safely be applied
- Serious medical comorbidities precluding radiotherapy. These include, but are not limited to. the following:
  - Interstitial lung disease in patients requiring thoracic radiation
  - Active Crohn disease in patients where the GI tract will receive radiotherapy, or active ulcerative colitis where the bowel will receive radiotherapy
  - Connective tissue disorders such as lupus or scleroderma
  - Known genetic disorders associated with increased toxicity to radiation therapy, e.g., ataxia telangiectasia.
- Substantial overlap with a previously treated radiation volume:

  Prior radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein.

  For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses. All such cases must be discussed with the responsible radiotherapy investigator at the site. *The Medical Monitor is available to advise as needed.*

  Lesions that have been treated with radiotherapy within the last 6 months should not be radiated

Section 8: Additional Exclusion Criteria for Atezo + Pem + Carbo Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Pem + Carbo arm during Stage 2:

- Histologically or cytologically confirmed squamous NSCLC
- History of allergic reaction to carboplatin, other platinum-containing compounds, or pemetrexed
- Creatinine clearance < 45 mL/min (calculated using the Cockcroft-Gault formula)

Section 9: Additional Exclusion Criteria for Atezo + Gem + Carbo Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Gem + Carbo arm during Stage 2:

- Histologically or cytologically confirmed non-squamous NSCLC

- History of allergic reaction to carboplatin, other platinum-containing compounds, or gemcitabine
- Creatinine clearance $<$45 mL/min (calculated using the Cockcroft-Gault formula)
- Radiation therapy within 7 days prior to initiation of gemcitabine

Section 10: Additional Exclusion Criteria for Atezo + Lina Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Linagliptin arm during Stage 2:

- Known diagnosis of Type 2 diabetes mellitus currently treated with a dipeptidyl peptidase-4 inhibitor
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications

END OF STUDY

The end of this study is defined as the date when the last patient completes the last visit, including survival follow-up visits conducted by telephone or on-site visit.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 7 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products for this study are atezolizumab, cobimetinib, evolocumab, docetaxel, ipatasertib, pemetrexed, carboplatin, gemcitabine, linagliptin, bevacizumab, and sacituzumab govitecan.

TEST PRODUCTS (INVESTIGATIONAL DRUGS)

Atezolizumab plus Cobimetinib

Patients in the Atezo + Cobi arm will receive treatment as outlined in Table 6 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 6 Treatment Regimen for Atezo + Cobi Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Cobimetinib 60 mg by mouth once daily on Days 1–21 • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Cobi = atezolizumab plus cobimetinib.

Atezolizumab plus Evolocumab

Patients in the Atezo + Evo arm will receive treatment as outlined in Table 7 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 7 Treatment Regimen for Atezo + Evo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Evolocumab 140 mg SC on Days 1 and 15

Atezo + Evo = atezolizumab plus evolocumab.

Atezolizumab plus Ipatasertib

Patients in the Atezo + Ipat arm will receive treatment as outlined in Table 8 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 8 Treatment Regimen for Atezo + Ipat Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Ipatasertib 400 mg by mouth once daily on Days 1–21 • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Ipat = atezolizumab plus ipatasertib.

Atezolizumab plus Sacituzumab Govitecan

Patients in the Atezo + SG arm will receive treatment as outlined in Table 9 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 9 Treatment Regimen for Atezo + SG Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 [a] • Atezo 1200 mg IV on Day 1 [b]

Atezo + SG = atezolizumab plus sacituzumab govitecan.

[a] There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[b] The atezolizumab infusion should be initiated approximately 60 minutes following completion of the Sacituzumab govitecan infusion.

Atezolizumab plus Pemetrexed plus Carboplatin

Patients in the Atezo + Pem + Carbo arm will receive treatment as outlined in Table 10. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Patients will continue pemetrexed until unacceptable toxicity or disease progression per RECIST v1.1. Carboplatin will be administered for the first four or six cycles, depending on local clinical practice. However, carboplatin will be discontinued for patients who experience unacceptable toxicity or disease progression per RECIST v1.1.

Table 10 Treatment Regimen for Atezo + Pem + Carbo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Pemetrexed 500 mg/m^2 IV on Day 1 of each cycle • Carboplatin AUC 6 mg/mL/min (Calvert formula dosing) IV on Day 1 of the first four or six cycles

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve.

Atezolizumab plus Gemcitabine plus Carboplatin

Patients in the Atezo + Gem + Carbo arm will receive treatment as outlined in Table 11. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Gemcitabine and carboplatin will be administered for the first four or six cycles, depending on local clinical practice. However, gemcitabine and carboplatin will be discontinued for patients who experience unacceptable toxicity or disease progression per RECIST v1.1.

Table 11 Treatment Regimen for Atezo + Gem + Carbo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of the first four or six cycles • Carboplatin AUC 5 mg/mL/min (Calvert formula dosing) IV on Day 1 of the first four or six cycles

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve.

Atezolizumab plus Docetaxel

Patients in the Atezo + Docetaxel arm will receive treatment as outlined in Table 12. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) and will continue docetaxel until unacceptable toxicity or radiographic disease progression per RECIST v1.1.

Table 12 Treatment Regimen for Atezo + Docetaxel Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Docetaxel 75 mg/m^2 IV over 1 hour on Day 1 of each cycle

Atezo + Docetaxel = atezolizumab plus docetaxel.

Atezolizumab plus Linagliptin

Patients in the Atezo + Linagliptin arm will receive treatment as outlined in Table 13 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 13 Treatment Regimen for Atezo + Lina Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Linagliptin 5 mg by mouth once daily

Atezo + Lina = atezolizumab plus linagliptin.

Atezolizumab plus Bevacizumab

Patients in the Atezo + Bev arm will receive treatment as outlined in Table 14 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 14 Treatment Regimen for Atezo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev = atezolizumab plus bevacizumab.

Atezolizumab plus Bevacizumab plus Radiotherapy

Patients in the Atezo + Bev + RTx arm will receive treatment as outlined in Table 15 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 15 Treatment Regimen for Atezo + Bev + RTx Arm

Radiotherapy	
Treatment Duration	Dose and Fractionation
Up to 21 days (±5 days, including simulation, contouring, and planning)	8Gy × 3
Systemic Therapy	
Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy.

COMPARATORS

Atezolizumab (Control for Cohort 1)

Patients in the Atezo arm will receive treatment as outlined in Table 16 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

Table 16 Treatment Regimen for Atezo Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Atezo 1200 mg IV on Day 1 of each cycle

Atezo = atezolizumab.

Docetaxel (Control for Cohort 2)

Patients in the docetaxel arm will receive treatment as outlined in Table 17 until unacceptable toxicity or disease progression per RECIST v1.1.

Table 17 Treatment Regimen for Docetaxel Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Docetaxel 75 mg/m^2 IV over 60 minutes on Day 1 of each cycle

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

For patients in the Atezo + Ipat arm, loperamide will be administered daily as prophylaxis for diarrhea in the first cycle. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgment.

For patients in the Atezo + SG arm, premedication for prevention of infusion-related reactions and chemotherapy-induced vomiting is recommended. Premedicate with antipyretics and H_1 and H_2 blockers prior to infusion; corticosteroids may be used for subjects who have had prior infusion-related reactions. Premedicate with a two- or three-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist), as well as other drugs as indicated.

To reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions, patients in the docetaxel arm and patients in the Atezo + Docetaxel arm should also be premedicated with corticosteroids (according to local practice [e.g., 8 mg of oral dexamethasone administered twice daily] for 3 days, starting 1 day prior to docetaxel administration).

Patients in the Atezo + Pem + Carbo arm should receive corticosteroid, folic acid, and vitamin B-12 premedication for pemetrexed according to the local standard of care and manufacturer's instructions.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy endpoint is objective response during Stage 1, as defined in Table 1. Patients with missing or no response assessments will be classified as non-responders.

Objective response rate (ORR), defined as the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% confidence intervals (Clopper Pearson method). The difference in ORR between the experimental arms and the corresponding control arm will also be calculated, along with 95% confidence intervals.

DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with metastatic NSCLC.

Approximately 255–435 patients will be randomly allocated to the control and experimental arms during the study.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm. With approximately 15 patients with serial biopsies in each arm, an 80% two-sided confidence interval for a 30% increase in $CD8^+$ T cells in the center of the tumor would be 22.8%, 37.2%, assuming a standard deviation of 0.20 for the difference in $CD8^+$ T cells between paired samples (i.e., baseline vs. on-treatment samples, baseline vs. post-progression samples, or on-treatment vs. post-progression samples).

INTERIM ANALYSES

It is anticipated that interim analyses will be conducted over the course of the study, with the earliest (Stage 1) interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase, approximately 15 patients have been enrolled in the control arm for that same cohort, and patients have been followed for a minimum of 6 weeks for the primary endpoint analysis (ORR). If no complete or partial responses are observed in an experimental arm, enrollment in that arm will be stopped. Otherwise, a posterior probability may be used to guide further enrollment in a treatment arm based on an interim analysis of clinical activity in the experimental arm compared with the control arm.

If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be further enrollment of 25 additional patients in the experimental arm.

If enrollment in the Atezo + Docetaxel arm is stopped in Stage 1 on the basis of the interim analysis, enrollment in the Atezo + Docetaxel arm in Stage 2 will be paused to allow for further evaluation.

An interim analysis will also be conducted after approximately 15 patients have been enrolled in a Stage 2 treatment arm and followed for a minimum of 6 weeks. If no complete or partial responses are observed after at least 15 patients have been enrolled and followed for a minimum of 6 weeks in the Atezo + Pem + Carbo arm, the Atezo + Gem + Carbo arm, the Atezo + Lina arm, or the Atezo + Docetaxel arm (Stage 2), further enrollment in that arm will be stopped.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody, also known as anti-therapeutic antibody
ALP	alkaline phosphatase
AML	acute myeloid leukemia
Atezo	atezolizumab
AUC	area under the concentration–time curve
CCOD	clinical cutoff date
CEA	carcinoembryonic antigen
CIT	cancer immunotherapy
CNS	central nervous system
Cobi	cobimetinib
COVID-19	*coronavirus disease 2019*
CrCL	creatinine clearance
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DOR	duration of response
DPP-4	dipeptidyl peptidase-4
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
Evo	evolocumab
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HeFH	heterozygous familial hypercholesterolemia
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IFN-γ	Interferon-γ

Abbreviation	Definition
IHC	immunohistochemistry
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
Ipat	ipatasertib
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LDL-C	LDL bound cholesterol
LDLR	LDL receptor
Lina	linagliptin
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MBP	microprecipitated bulk powder
MDM2	murine double minute 2
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition (scan)
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	Proprotein convertase
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks

Abbreviation	Definition
QD	once daily
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RTx	radiotherapy
RVO	retinal vein occlusion
SARS-CoV-2	*severe acute respiratory syndrome coronavirus-2*
SBRT	stereotactic body radiotherapy
SOC	Scientific Oversight Committee
SG	sacituzumab govitecan
T3	triiodothyronine
T4	thyroxine
TCR	T-cell receptor
TNF-α	tumor necrosis factor-α
TPS	tumor proportion score
TROP-2	trophoblast cell-surface antigen 2
ULN	upper limit of normal
WBRT	whole-brain radiotherapy
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON LUNG CANCER

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011). In 2012, it was estimated that there were 313,000 new cases of lung cancer and 268,000 lung cancer deaths in Europe (GLOBOCAN 2012). In the United States, there were an estimated 221,200 new cases of lung cancer and 158,040 lung cancer deaths in 2015 (Siegel et al. 2015).

Non–small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Howlader et al. 2015). NSCLC can be divided into two major histologic types: adenocarcinoma and squamous cell carcinoma (Travis et al. 2011). Adenocarcinoma histology accounts for more than half of all NSCLC, while squamous cell histology accounts for approximately 25% of NSCLC (Langer et al. 2010). There are recognized clinical differences in disease characteristics between adenocarcinoma and squamous NSCLC. First, squamous tumors commonly present in the central airways and typically remain localized in the bronchial epithelium (Hirsch et al. 2008), whereas non-squamous tumors are more commonly located in the lung parenchyma distal to the central airways. The remaining cases of NSCLC are represented by large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and poorly differentiated histology.

Genetic changes that have prognostic and/or predictive significance in NSCLC include mutations in the *EGFR* gene, rearrangements in the *ALK* gene, and mutations in the *KRAS* gene. The rates of these mutations differ between squamous cell carcinoma and adenocarcinoma. For example, *EGFR* kinase domain mutations have been reported in 10%–40% of patients with adenocarcinoma NSCLC but are infrequently observed in squamous NSCLC (Herbst et al. 2008). Similarly, the *ALK* fusion oncogene, recognized as a driver of lung tumorigenesis, is observed in approximately 7% of patients with adenocarcinoma but is very rare in the squamous histology (Herbst et al. 2008; Langer et al. 2010). In addition, *KRAS* mutations are very rare in squamous NSCLC, while they can be observed in up to 30% of cases of adenocarcinoma NSCLC (Travis et al. 2011).

The overall 5-year survival rate for advanced disease is 2%–4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced-stage disease at the time of initial diagnosis, poor performance status, and history of unintentional weight loss. More than half of patients with NSCLC are diagnosed with distant disease, which directly contributes to poor survival prospects. Therefore, there is a high unmet need for improved medical intervention.

1.2 TREATMENT FOR NSCLC

1.2.1 Previously Untreated NSCLC without an *EGFR* Mutation or *ALK* Rearrangement

For patients without a driver mutation that confers sensitivity to a targeted agent, the globally recognized standard of care for inoperable Stage IIIB or IV NSCLC is platinum-based chemotherapy for four to six cycles followed by maintenance treatment until progression. This standard of care applies to both non-squamous and squamous NSCLC (Pfister et al. 2004; D'Addario et al. 2010; de Marinis et al. 2011; NCCN 2014). Agents that have been partnered with either cisplatin or carboplatin include taxanes (paclitaxel or docetaxel), vinorelbine, gemcitabine, pemetrexed, and bevacizumab. Combinations of these drugs with platinum analogs are superior to single-agent therapy and have been shown to prolong survival (Azzoli et al. 2009).

In a Phase III Eastern Cooperative Oncology Group (ECOG) study of four platinum-based doublets (gemcitabine + cisplatin, docetaxel + cisplatin, paclitaxel + carboplatin, and paclitaxel + cisplatin) in patients with Stage IIIB or IV NSCLC who had not previously received chemotherapy (Schiller et al. 2002), the median survival rate was approximately 8 months for all four arms. Paclitaxel + carboplatin was chosen as the reference regimen for ECOG's future studies because of its more favorable toxicity profile. The benefit conferred by platinum-based chemotherapy regimens appears to have reached a plateau in objective response rate (ORR) (approximately 15%–25%) and median survival (7–11 months).

Immune checkpoint inhibitors, including programmed death ligand 1/programmed cell death protein 1 (PD-L1/PD-1) blocking antibodies, have recently emerged as a therapeutic option for first-line treatment of metastatic NSCLC. Pembrolizumab, a PD-1 inhibitor, is approved for the first-line treatment of metastatic NSCLC in patients whose tumors have PD-L1 expression on at least 50% of tumor cells (tumor proportion score [TPS] $\geq$ 50%) with no *EGFR* or *ALK* gene aberrations. In a Phase III study (KEYNOTE-024), the estimated rate of overall survival (OS) at 6 months was 80.2% for patients receiving pembrolizumab monotherapy compared with 72.4% for patients receiving platinum-based chemotherapy; the median OS was not reached in either group. OS was significantly longer in the pembrolizumab arm than in the chemotherapy arm (hazard ratio = 0.60; p = 0.005) (Reck et al. 2016).

For most patients with previously untreated advanced-stage NSCLC with low PD-L1 expression (TPS < 50%), the standard of care remains platinum-based chemotherapy. For non-squamous disease, the platinum (i.e., cisplatin or carboplatin) is typically combined with either a taxane or pemetrexed, with or without bevacizumab. For squamous disease, the platinum is combined with gemcitabine.

The combination of pembrolizumab with carboplatin/cisplatin and pemetrexed was approved by the U.S. Food and Drug Administration (FDA) for patients with non-squamous NSCLC based on the Phase II study KEYNOTE-021. The results have been confirmed for patients with non-squamous NSCLC in the Phase III study KEYNOTE-189. The triplet combination demonstrated a significantly longer median OS in the intent-to-treat population than chemotherapy alone (HR = 0.49; $p < 0.0001$). Median progression-free survival (PFS) was also significantly longer for the experimental arm (8.8 months vs. 4.9 months; HR = 0.52, $p < 0.0001$) (Gandhi et al. 2018). This combination may replace platinum-based chemotherapy regimens as a standard of care for patients who were previously untreated with advanced-stage non-squamous NSCLC with low PD-L1 expression.

In the Phase III study KEYNOTE-407, the combination of pembrolizumab with carboplatin plus either paclitaxel or nanoparticle albumin-bound (nab)-paclitaxel demonstrated a statistically significant OS benefit as compared with the control arm of carboplatin plus nab-paclitaxel (HR = 0.64; 95% CI: 0.49, 0.85; $p < 0.001$). The OS benefit was consistent across all levels of PD-L1 expression. The median PFS was 6.4 months (95% CI: 6.2, 8.3) in the pembrolizumab combination group and 4.8 months (95% CI: 4.3, 5.7) in the placebo combination group (HR = 0.56; 95% CI: 0.45, 0.70; $p < 0.001$) (Paz-Ares et al. 2018). On the basis of these results, the U.S. FDA has approved the combination of pembrolizumab plus carboplatin plus nab-paclitaxel for the first-line treatment of patients with squamous NSCLC.

More recently, in the Phase III IMpower150 study, the combination of atezolizumab and bevacizumab plus carboplatin and paclitaxel demonstrated a significant increase in PFS compared with bevacizumab plus carboplatin and paclitaxel in patients with metastatic non-squamous NSCLC (ITT population: HR = 0.62; 95% CI: 0.52, 0.74; $p < 0.001$). Furthermore, a significant and clinically meaningful improvement in median OS was observed for the atezolizumab-containing group at the second interim analysis (19.2 months vs. 14.7 months; stratified HR = 0.78; 95% CI, 0.64, 0.96; $p = 0.02$) (Socinski et al. 2018).

1.2.2 Previously Treated NSCLC

With the approval of immune checkpoint inhibitors as first-line treatment of advanced NSCLC in patients with high PD-L1 expression, the treatment algorithm for this patient population is changing. Platinum-based chemotherapy will increasingly be used as second line treatment for patients who experience disease progression during or following treatment with an immune checkpoint inhibitor. Furthermore, immune checkpoint inhibitors combined with platinum-based chemotherapy are expected to be used for patients with low PD-L1 expression or an unknown PD-L1 status who experienced disease progression during or following treatment with a platinum-doublet.

To date, three immune checkpoint inhibitors have been approved for patients with metastatic NSCLC who experience disease progression during or following

platinum-containing chemotherapy: nivolumab (PD-1 inhibitor), pembrolizumab (PD-1 inhibitor), and atezolizumab (PD-L1 inhibitor). Pembrolizumab is approved for patients whose tumors express PD-L1 (TPS $\geq$1%), whereas PD-L1 expression is not a requirement for patients receiving treatment with nivolumab and atezolizumab.
For nivolumab, the median OS was 9.2 months for patients with squamous histology and 12.2 months for patients with non-squamous histology (Opdivo® U.S. Package Insert).
For pembrolizumab, the median OS was 10.4 months for patients treated at 2 mg/kg every 3 weeks (Q3W) and 12.7 months for patients treated at 10 mg/kg Q3W (squamous and non-squamous histology combined) (Keytruda® U.S. Package Insert).
For atezolizumab, the median OS was 13.8 months (squamous and non-squamous histology combined) (Tecentriq® U.S. Package Insert).

In addition to immune checkpoint inhibitors and platinum-based chemotherapy, docetaxel and pemetrexed are approved for patients with metastatic NSCLC who experience disease progression during or following prior chemotherapy. Docetaxel was associated with an estimated median OS of 6–10 months (Stinchcombe and Socinski 2008; Ramlau et al. 2012). Pemetrexed had improved PFS and OS compared with docetaxel in patients with non-squamous histologies, thus limiting its approval to patients with non-squamous NSCLC (Scagliotti et al. 2009).

The choice of agent in the second- or third-line setting depends on a number of factors, including tumor histology, comorbidities, toxicity from previous treatments, toxicity profile for a given agent, smoking history, and patient preference. Overall, the benefit–risk profile of these therapies has been disadvantaged both by limited survival benefit and significant toxicities such as myelosuppression and neuropathy (docetaxel) and diarrhea (pemetrexed) (Stinchcombe and Socinski 2008).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will enroll two patient populations with metastatic NSCLC and significant unmet medical need: patients with high tumor PD-L1 expression (TPS $\geq$50%, as determined through use of the Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay) who have received no prior systemic therapy for metastatic NSCLC (Cohort 1) and patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression (Cohort 2). While single-agent immune checkpoint inhibitors have shown superiority over platinum-based chemotherapy in previously untreated patients whose tumors have high PD-L1 expression, less than half of these patients experience an objective response (Reck et al. 2016). The combination of agents targeting different immune evasion mechanisms may increase response rates in this population. Given the relatively poor prognosis, limited treatment options, and potential toxicities associated with treatments for patients

in Cohort 2, this population is in need of treatment options and therefore considered appropriate for trials of novel therapeutic candidates.

Cancer immunotherapy (CIT) has demonstrated clear clinical efficacy, with significant survival benefit observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by targeting T-cell inhibitory factors such as PD-L1/PD-1. While these targets have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is necessary for the generation of a continuous anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune-evasion mechanisms. Thus, the need to identify and circumvent the various factors that account for the absence of, or escape from, an effective anti-cancer immune response will be critical for propagating cancer immunity and advancing the field of CIT, most likely through combined cancer immunotherapy regimens.

This randomized Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with NSCLC. The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. Enrollment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a control arm. Moreover, patients who experience disease progression with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of immune escape mechanisms in patients who fail to respond to, or experience disease progression during, treatment with a CIT or chemotherapy regimen.

The target and proposed mechanism-of-action classification for each experimental investigational medicinal product (IMP) is summarized in Table 1. The control and experimental treatment regimens are described in Section 3.1 (see Table 4 and Table 6). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in Table 4 and Table 6.

Table 1 Target and Proposed Mechanism-of-Action Classification for Experimental Investigational Medicinal Products

Experimental IMP	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Immune checkpoint inhibitor
Cobimetinib	MEK	Kinase inhibitor, T-cell survival and accumulation, immune recognition of tumor cells, tumor microenvironment recruitment [a]
Ipatasertib	Akt	Kinase inhibitor, tumor cell death, reversal of T cell-mediated IT resistance [b]
Linagliptin	DPP-4	DPP-4 inhibitor; restores intratumoral chemotactic gradients and immune cell recruitment [d]
Bevacizumab	VEGF	Angiogenesis inhibitor, recruitment of T cells to the tumor microenvironment [e]
Docetaxel	Tubulin	Anti-mitotic chemotherapy agent
Sacituzumab govitecan	TROP-2	Tumor cell-targeted topoisomerase-I inhibitor, causes tumor cell death [f]
Evolocumab	PCSK9	PCSK9 inhibitor, increases MHC-I expression on tumour cells [g]

CEA = carcinoembryonic antigen; CRS = cytokine-release syndrome; DPP-4 = dipeptidyl peptidase-4; IL-6R = interleukin-6 receptor; IMP = investigational medicinal product; MDM2 = murine double minute 2; MHC-I = major histocompatibility complex class-I; PCSK9 = proprotein convertase subtilisin/kexin type 9; TROP-2 = trophoblast cell-surface antigen 2; VEGF = vascular endothelial growth factor.

[a] Ebert et al. 2016.

[b] Peng et al. 2016.

[c] Cekic and Linden 2016.

[d] Barreira da Silva et al. 2015.

[e] Wallin et al. 2016.

[f] Heist et al. 2017

[g] Liu et al. 2020

1.4 COVID-19 BENEFIT–RISK ASSESSMENT

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of SARS-CoV-2 infection.

A possible consequence of immune checkpoint inhibition may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses (Wykes- and Lewin 2018). In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are

insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS-CoV-2 infection while receiving immune checkpoint inhibitor therapies (e.g., atezolizumab). At this time, there is insufficient evidence for causal association between immune checkpoint inhibitor therapies and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with immune checkpoint inhibitor therapies and clinical and radiologic features for SARS-CoV-2–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors and chemotherapy), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving cancer immunotherapy, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving cancer immunotherapy to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When

administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with metastatic NSCLC. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 2) and Stage 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart during Stage 1, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • OS after randomization, defined as the time from randomization to death from any cause • OS at specific timepoints (e.g., 6 months) • DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1

ADA=anti-drug antibody; DOR=duration of response; eCRF=electronic Case Report Form; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objectives (cont.)	**Corresponding Endpoints (cont.)**
• To evaluate potential effects of ADAs during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.8) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form;NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented objective response during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Disease control, defined as stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each (as appropriate) drug at specified timepoints
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Exploratory Immunogenicity Objectives	Corresponding Endpoints
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline
• To evaluate potential effects of ADAs during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK, endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.8) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; DOR = duration of response; eCRF = electronic Case Report Form;NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

3. STUDY DESIGN

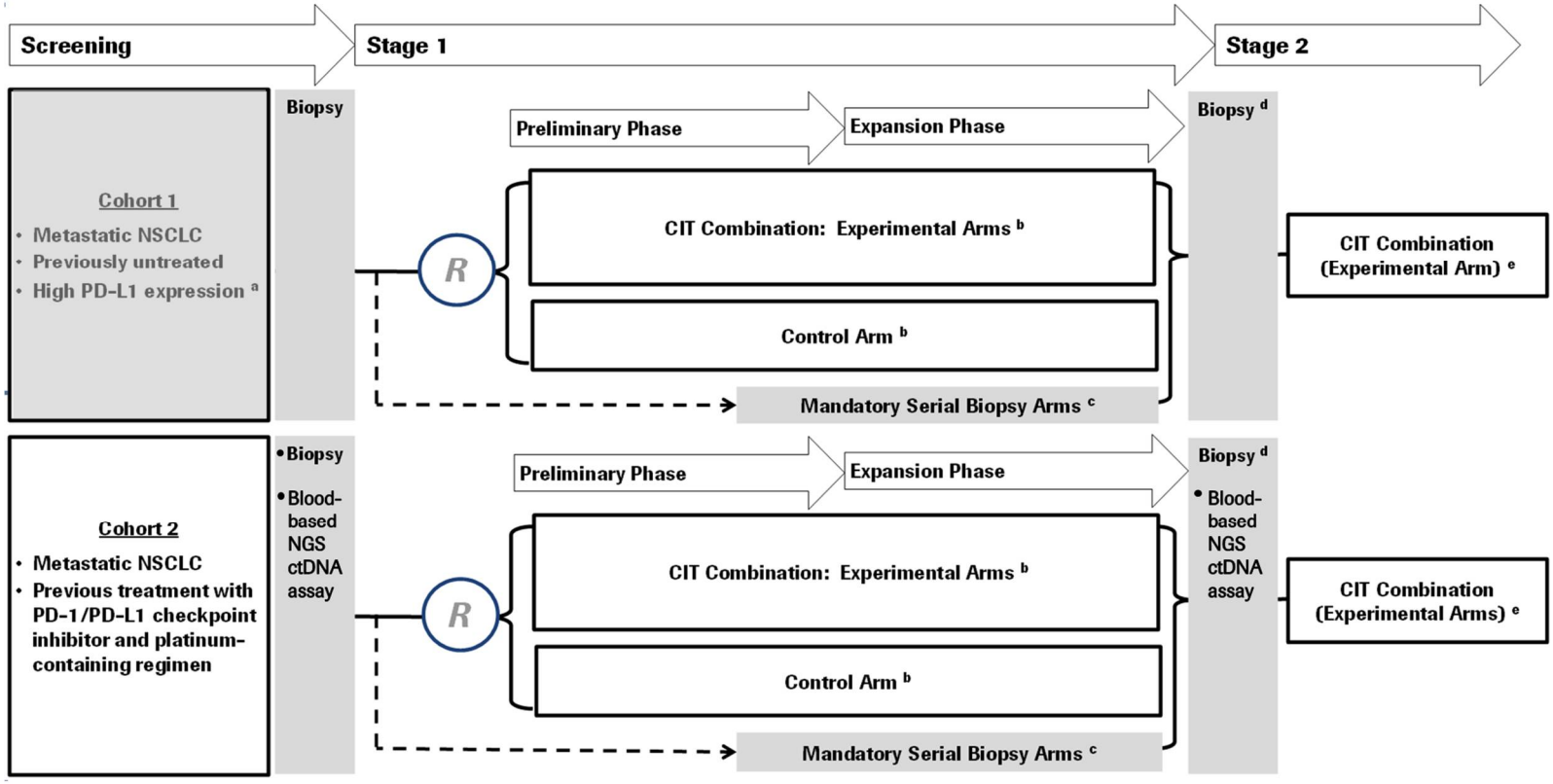
3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, open-label, multicenter, randomized, umbrella study in patients with metastatic NSCLC. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status).
Two cohorts will be enrolled in parallel in this study: Cohort 1 will consist of patients with high tumor PD-L1 expression (TPS $\geq$ 50%, as determined through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay) who have received no prior systemic therapy for metastatic NSCLC, and Cohort 2 will consist of patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in

combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression (see Figure 1). In each cohort, eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Section 3.1.1). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2; see Section 3.1.3).

Because the treatment landscape for first-line metastatic NSCLC has evolved since the initiation of this study, with new and highly effective treatment options being available in this setting, patient enrollment into Cohort 1 has been suspended as of November 2018, and patients will no longer be enrolled into Cohort 1. Patients already enrolled in Cohort 1 will continue to be treated and monitored per protocol and may be eligible for Stage 2 treatment.

Figure 1 General Study Design



CIT = cancer immunotherapy; ctDNA = circulating tumor DNA; IHC = immunohistochemistry; NGS = next-generation sequencing; NSCLC = non–small cell lung cancer; R = randomization.

[a] PD-L1 expression on at least 50% of tumor cells, as determined through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay.

[b] Refer to Table 4 for a summary of available Stage 1 treatment regimens in Cohorts 1 and 2.

[c] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

[d] A biopsy will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1, or loss of clinical benefit as determined by the investigator (if deemed clinically feasible by the investigator).

[e] Refer to Table 6 for a summary of available Stage 2 treatment regimens in Cohorts 1 and 2..

3.1.1 Stage 1

During Stage 1, patients in Cohort 1 will be randomly assigned to a control arm (atezolizumab [Atezo]) or an experimental arm consisting of atezolizumab in combination with cobimetinib (Atezo + Cobi) and patients in Cohort 2 will be randomly assigned to a control arm (docetaxel) or an experimental arm consisting of atezolizumab in combination with cobimetinib (Atezo + Cobi), ipatasertib (Atezo + Ipat), bevacizumab (Atezo + Bev), bevacizumab and radiotherapy (Atezo + Bev + RTx), docetaxel (Atezo + Docetaxel), sacituzumab govitecan (Atezo + SG), or evolocumab (Atezo + Evo) (see Figure 2 and Figure 3). Details on the treatment regimens for Stage 1 are provided in Appendix 7–Appendix 12 , Appendix 16, and Appendix 18–Appendix 19 as specified in Table 4. *Table 5 lists Stage 1 treatment arms for which enrollment and patient follow-up has been completed.*

Approximately 255–435 patients will be enrolled during Stage 1. Enrollment within the experimental arms will take place in two phases: a preliminary phase followed by an expansion phase. Approximately 40 patients will be enrolled in the ipatasertib-containing arm during the preliminary phase to ensure a sufficient number of patients with PI3K/Akt pathway alterations, and 40 patients will be enrolled in the bevacizumab-containing arms during the preliminary phase to ensure a sufficient number of patients with STK11/LKB1 mutations. Thirty patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low trophoblast cell-surface antigen 2 (TROP-2) expression. Twenty patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high proprotein convertase subtilisin/kexin type 9 (PCSK9) expression (PCSK9-high) and low PCSK9 expression (PCSK9-low). Additional patients may be enrolled in the Atezo + Evo arm to ensure that at least 10 patients with high PCSK9 expression are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase. Fifteen patients will be enrolled in all other experimental arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may decide to delay or suspend enrollment within a given treatment arm. The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see Section 3.1.2 for details). Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be enrolled to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol.

Patients will be randomly assigned to treatment arms, with the exception of the mandatory serial biopsy arms, and the randomization ratio will depend on the number of

experimental arms that are available (e.g., if an arm is added or enrollment in an arm is suspended, pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on treatment assignment and randomization are provided in Section 4.2.

Table 4 Stage 1 Treatment Regimens

Cohort (Enrollment Status)	Study Treatment	No. of Patients [a]		Appendix
		Preliminary Phase	Expansion Phase [b, c]	
1 (not enrolling [d, e])	Atezo	Variable [a]		Appendix 7
	Atezo + Cobi [f]	15	25	Appendix 8
2 (enrolling [d])	Docetaxel	Variable [a]		Appendix 10
	Atezo + Cobi [f]	15	25	Appendix 8
	Atezo + Evo	20 [g]	25	Appendix 9
	Atezo + Ipat	40	25	Appendix 11
	Atezo + Docetaxel [f]	15	25	Appendix 16
	Atezo + Bev	40	25	Appendix 18
	Atezo + Bev + RTx	40	25	Appendix 19
	Atezo + SG	30 [h]	25	Appendix 12

Atezo = atezolizumab; Bev = bevacizumab; CEA = carcinoembryonic antigen; Cobi = cobimetinib; Evo = evolocumab; Ipat = ipatasertib; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTx = radiotherapy; SG = sacituzumab govitecan; TROP-2 = trophoblast cell-surface antigen 2.

[a] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 35% of patients will be randomly allocated to a control arm (see Section 4.2 for details).

[b] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients will be enrolled in that arm during the expansion phase.

[c] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

[d] The Sponsor may decide to delay or suspend enrollment within a given treatment arm. Thus, all listed experimental arms may not be open for enrollment at the same time.

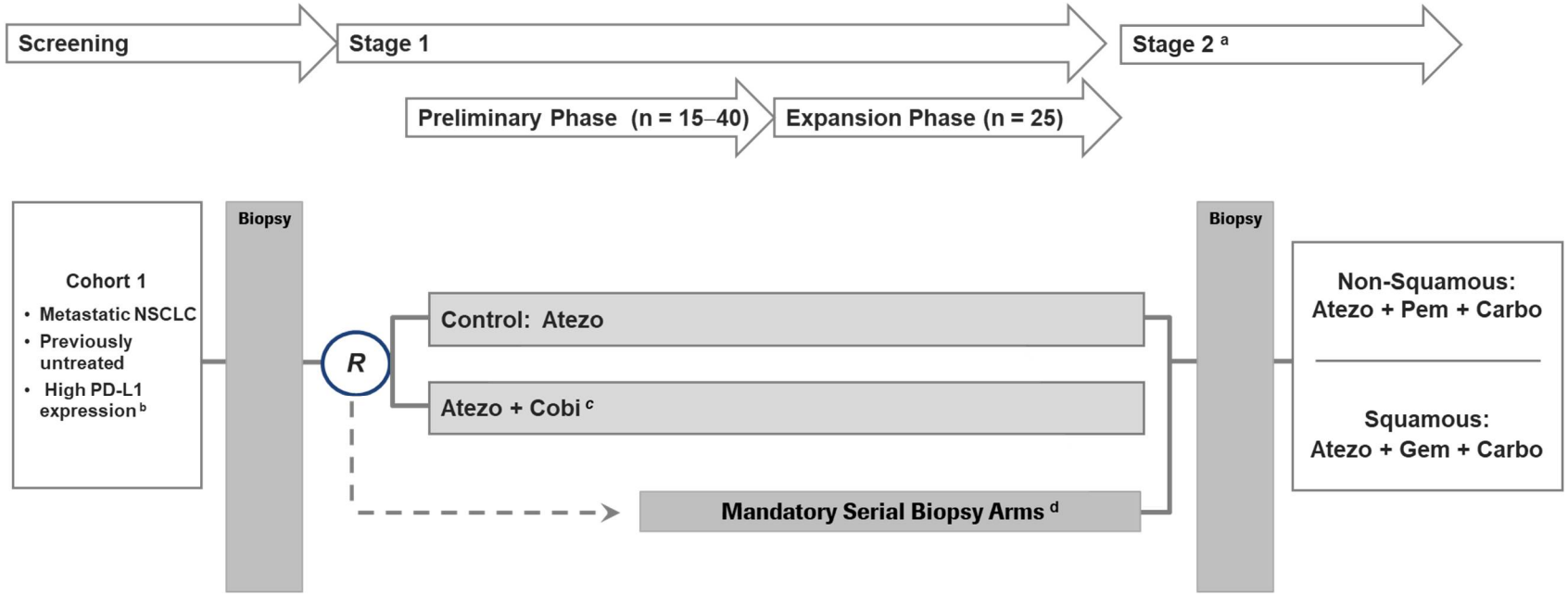
[e] Further enrollment in Cohort 1 has been suspended as of November 2018 (see Section 3.1.1 for details).

[f] This arm is closed and will be removed when the last patient discontinues from the study.

[g] Approximately 20 patients will be enrolled in the Atezo + Evo arm to ensure a sufficient number of patients with high PCSK9-expression (PCSK9-high) and low PCSK9 expression (PCSK9-low) to facilitate the evaluation of the benefit and risk in these subpopulations. Additional patients may be enrolled in the Atezo + Evo arm to ensure that at least 10 patients with high PCSK9 are included. No more than 30 patients will be enrolled in the Atezo + Evo arm in the preliminary phase.

[h] 30 patients will be enrolled in the Atezo + SG arm to ensure a sufficient number of patients with high, medium, and low TROP-2 expression to facilitate the evaluation of the benefit and risk of these subpopulations.

Figure 2 Detailed Study Design: Cohort 1



Atezo = atezolizumab; Carbo = carboplatin; Cobi = cobimetinib; Gem = gemcitabine; IHC = immunohistochemistry; n = number of patients; NSCLC = non–small cell lung cancer; Pem = pemetrexed; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

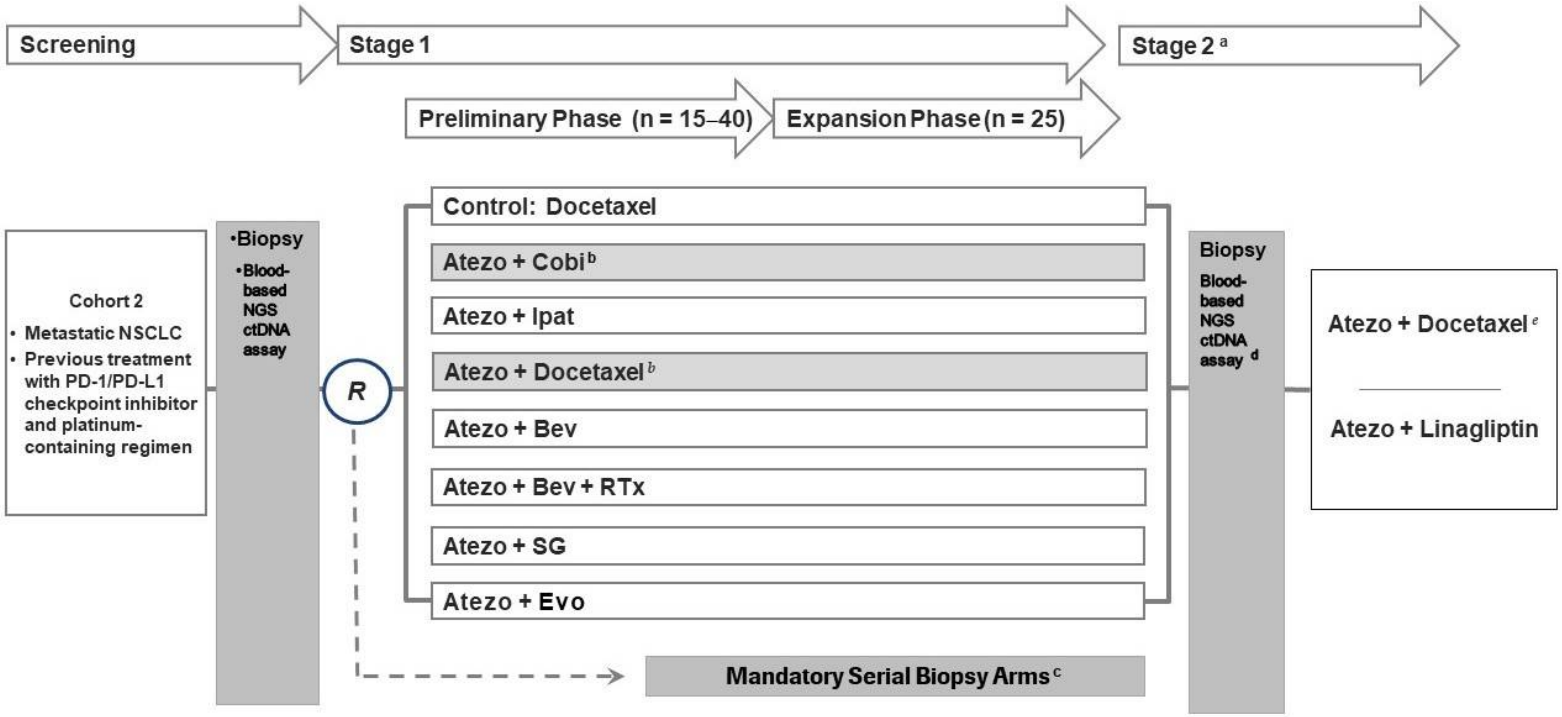
[a] Patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see Appendix 7–Appendix 12, Appendix 16, Appendix 18, and Appendix 19).

[b] PD-L1 expression on at least 50% of tumor cells, as determined through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay.

[c] This arm is closed and will be removed when the last patient discontinues from the study.

[d] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

Figure 3 Detailed Study Design: Cohort 2



Atezo = atezolizumab; Bev = bevacizumab: Cobi = cobimetinib: ctDNA = circulating tumor DNA; Evo = Evolocumab; Ipat = ipatasertib; Lina = linagliptin; n = number of patients; NGS = next generation sequencing; NSCLC = non–small cell lung cancer; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RTx = radiotherapy; SG = sacituzumab govitecan.

[a] Patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity during Stage 1 may be eligible to receive a different treatment combination during Stage 2, provided they meet the eligibility criteria. Details are provided in the respective appendix for each treatment arm (see Appendix 7–Appendix 12, Appendix 16, Appendix 18, and Appendix 19).

[b] This arm is closed and will be removed when the last patient discontinues from the study.

[c] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients at participating sites who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.2).

[d] A blood sample for the blood-based NGS ctDNA assay will only be collected at Stage 1 treatment discontinuation from patients enrolled in the following treatment arms: Docetaxel, Atezo + Ipat, Atezo + Docetaxel, Atezo + Bev, Atezo + Bev + RTx, Atezo + SG, and Atezo + Evo.

[e] *This arm is currently not enrolling.*

Table 5 Treatment Arms with Completed Follow-Up

Stage	Cohort	Study Treatment	No of Patients Enrolled		Protocol Versions Describing Arm
			Preliminary Phase	Expansion Phase	
1	1	Atezo + RO6958688	1	0	1–12
1	2	Atezo + RO6958688	1	0	1–12
1	*2*	*Atezo + CPI-444*	*16*	*0*	*1–13*

Atezo = atezolizumab

Patients in the docetaxel control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 1). Patients in the atezolizumab control arm and the atezolizumab combination arms will be treated until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Patients in the atezolizumab plus docetaxel arm will continue to receive docetaxel until unacceptable toxicity or disease progression per RECIST v1.1; atezolizumab can be continued until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease. Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with CITs (such as atezolizumab), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet the criteria for disease progression per RECIST v1.1 while receiving treatment with a CIT drug will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

3.1.2 Mandatory Serial Biopsy Arms at Participating Sites

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial

biopsy arm at the time that arm is open for expansion. This arm will consist of patients at participating sites who are willing to undergo an on-treatment biopsy.

Enrollment in a mandatory serial biopsy arm is contingent upon the review and approval of mandatory serial biopsies by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for mandatory serial biopsies, this section of the protocol (Section 3.1.2) will not be applicable at that site. The objective of the mandatory serial biopsy arms is to analyze serial tissue samples (including pre-treatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Biomarkers may include those that inform stromal and immune biology (Turley et al. 2015).

Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory biopsy arm is open within Cohort 1 or Cohort 2, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm. However, the number of patients will be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to a total of approximately 15 patients per CIT combination within each cohort.

Patients enrolled in a mandatory biopsy arm will undergo the same assessments as other patients receiving the same treatment combination but will have an additional mandatory on-treatment biopsy at Week 4 ($\pm$1 week) after initiation of CIT combination treatment (if deemed clinically feasible by the investigator). Details about the timing of biopsy sample collection are provided in the schedule of activities for each arm (see Appendix 7–Appendix 12, Appendix 16, Appendix 18, and Appendix 19).

To be eligible for a mandatory serial biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies $\geq$1 cm apart.

Patients enrolled in a mandatory serial biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

3.1.3 Stage 2

During Stage 1, patients who experience disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator (for details, see Section 3.1.1), or unacceptable toxicity may be eligible to receive a different treatment combination during Stage 2 as outlined in Table 6, provided they meet the eligibility criteria and a Stage 2 arm is open for enrollment. Details are provided in the respective appendix for each treatment arm (see Appendix 7–Appendix 12, Appendix 16, Appendix 18, and Appendix 19).

Study details specific to the Stage 2 treatment regimens are provided in Appendix 14–Appendix 17 as specified in Table 6.

Assignment to Stage 2 treatment arms will be determined by histologic type (non-squamous vs. squamous) for patients in Cohort 1 but not for patients in Cohort 2, as shown in Table 6. Patients in Cohort 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator.

Stage 2 treatment must begin within 3 months after a patient has experienced disease progression per RECIST v1.1 (docetaxel control arm), loss of clinical benefit (atezolizumab control arm and atezolizumab combination arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible.

Table 6 Stage 2 Treatment Regimens

Cohort (Enrollment Status)	Histologic Type	Study Treatment	Appendix
1 (not enrolling [a])	Non-squamous	Atezo + Pem + Carbo	Appendix 14
	Squamous	Atezo + Gem + Carbo	Appendix 15
2 (*not* enrolling [a])	Non-squamous or squamous	Atezo + Docetaxel [b]	Appendix 16
2 (enrolling [a])		Atezo + Lina	Appendix 17

Atezo = atezolizumab; Carbo = carboplatin; Gem = gemcitabine; Lina = linagliptin; Pem = pemetrexed.

[a] The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

[b] Patients who are enrolled in the Docetaxel control arm and the Atezo + Docetaxel arm in Stage 1 are not eligible to receive this study treatment in Stage 2.

The Sponsor may decide to discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.4 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Patients will undergo tumor assessments every 6 weeks (starting on Day 1 of Cycle 1) for the first 48 weeks and then every 6 or 12 weeks thereafter (see Section 4.5.5 and Appendix 7–Appendix 19 for details). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm *and the corresponding control arm* be submitted for evaluation by an independent review facility.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue *may* be discussed with the Medical Monitor. Tumor tissue will also be collected from patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (docetaxel control arm), or loss of clinical benefit as determined by the investigator (atezolizumab control arm and experimental arms) (if deemed clinically feasible by the investigator). Blood samples will be collected at screening and treatment discontinuation for blood-based next-generation sequencing (NGS) circulating tumor DNA (ctDNA) testing. For patients enrolled in a mandatory serial biopsy arm at participating sites, an additional tumor tissue sample will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.3.3 and details on tissue sample collection in Section 4.5.8).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and other therapeutic agents, blood samples will be obtained at various timepoints before and during study treatment administration.

On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate.

The schedule of activities for each treatment arm is presented in Appendix 7–Appendix 19.

3.1.5 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from Clinical Science, Safety Science, and Biostatistics. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.6 Scientific Oversight Committee

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in cancer immunotherapy who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The SOC may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit, including survival follow-up visits conducted by telephone or on-site visit.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 7 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Despite improvements in the first-line treatment of patients with metastatic NSCLC that have resulted in longer survival times and reduced disease-related symptoms, significant unmet medical need exists in this patient population.

The study will enroll two patient populations: patients with high tumor PD-L1 expression (TPS $\geq$50%, as determined through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay) who have received no prior systemic therapy for metastatic NSCLC (Cohort 1) and patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression (Cohort 2).

Atezolizumab and pembrolizumab have shown comparable 12-month OS rates and ORRs in previously untreated as well as in previously treated patients expressing high levels of PD-L1 on their tumors (Garon et al. 2015; Garassino et al. 2017; Reck et al. 2016; Rittmeyer et al. 2017). Cohort 1 will compare atezolizumab-based CIT combinations with atezolizumab alone in patients with high tumor PD-L1 expression (TPS $\geq$50%) who have received no prior systemic therapy for metastatic NSCLC. This design is expected to allow for rapid signal detection in a homogeneous patient population. Eligible patients will be required to have a high level of PD-L1 expression to ensure a population with a good probability of response.

Patients who experience progression during or following first-line treatment for metastatic NSCLC have an even more limited prognosis, with a median survival of approximately 8–9 months (Stinchcombe and Socinski 2008). Approved therapies are associated with significant toxicities (e.g., neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Thus, there is a continuing need for more efficacious, better-tolerated treatments. Therefore, Cohort 2 will compare CIT combinations with docetaxel alone in patients who experienced disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression. With the increasing use of checkpoint inhibitors as first-line or second-line therapy, this patient population is expected to increase over time and currently has no promising treatment options. It is therefore important to investigate a combination of agents targeting different tumor immune evasions mechanisms in this patient population.

3.3.2 Rationale for Immunotherapy-Based Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an apparent increase in tumor burden. This initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response has been termed pseudo-progression (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer

cells. Because of the potential for a response after pseudoprogression, this study will allow patients allocated to immunotherapy-based treatment arms to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 4.6.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (see Section 3.1.1 for details).

3.3.3 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline, during the study, and at Stage 1 discontinuation due to unacceptable toxicity, disease progression per RECIST v1.1, or loss of benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator), to enable analysis of biomarkers related to resistance, disease progression, and clinical benefit of study treatments. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and circulating tumor DNA) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker assay to help define future treatments and identify which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. Tumor tissue will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator), to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments.

Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of NGS and whole exome sequencing (WES) to identify somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to

developing adverse events, or can increase the knowledge and understanding of disease biology.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥18 years at the time of signing Informed Consent Form
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Life expectancy ≥ 3 months, as determined by the investigator
- Histologically or cytologically confirmed metastatic, non-squamous or squamous NSCLC

  Histologic classification may be based on tumor specimens collected prior to metastasis. Patients with tumors of mixed histology must be classified as non-squamous or squamous on the basis of the major histological component.
- For patients in Cohort 1: no prior systemic therapy for metastatic NSCLC

  Patients who received chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease in the neoadjuvant or adjuvant setting are eligible for the study if therapy was completed at least 6 months prior to initiation of study treatment.
- For patients in Cohort 2: disease progression during or following treatment for metastatic or locally advanced, inoperable NSCLC that consisted of a platinum-containing regimen and a PD-L1/PD-1 checkpoint inhibitor, given in combination as one line of therapy or as two separate lines of therapy (in either order), for a maximum of two prior lines of systemic therapy

  Patients with disease progression or recurrence within ≤6 months after completion of their definitive therapy for locally advanced disease may be allowed to participate in Cohort 2, provided their treatment for locally advanced inoperable NSCLC included a combination of at least a platinum-based chemotherapy (e.g., cisplatin or carboplatin) and PD-L1/PD-1 checkpoint inhibitor.

  Prior exposure to anti–CTLA-4 antibodies is allowed if used in combination with a PD-L1/PD-1 checkpoint inhibitor.

- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status by means of central testing

  Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue requires discussion with the Medical Monitor.

  A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least $15-16$ slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report to the designated central laboratory, once the patient is randomized. Refer to Section 4.5.8 for additional information on tumor specimens collected at screening.
- Availability of peripheral blood for NGS ctDNA testing
- For patients in Cohort 1: High tumor PD-L1 expression, defined as TPS $\geq 50\%$, as determined by a local laboratory through use of a protocol-specified assay, as described below:
  - U.S. sites: FDA-approved Dako PD-L1 IHC 22C3 pharmDx assay
  - Ex-U.S. sites: health authority–approved or CE-marked assay consisting of either the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 90 g/L (9.0 g/dL)

Patients may be transfused to meet this criterion.

- For patients in Cohort 1: AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5\times$ upper limit of normal (ULN) with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT $\leq 5\times$ ULN

  Patients with documented liver or bone metastases: ALP $\leq 5\times$ ULN

- For patients in Cohort 2: liver function test results that meet <u>one</u> of the following sets of criteria:

  a) AST, ALT, and ALP $\leq 2.5\times$ ULN

  b) AST and ALT $\leq 1.5\times$ ULN and ALP $\leq 5\times$ ULN

- For patients in Cohort 1: bilirubin $\leq 1.5\times$ ULN, with the following exception:

  Patients with known Gilbert disease: bilirubin level $\leq 3\times$ ULN

- For patients in Cohort 2: bilirubin $\leq 1.0\times$ ULN, with the following exception:

  Patients with known Gilbert disease: bilirubin level $\leq 3\times$ ULN

- Albumin ≥ 25 g/L (2.5 g/dL)
- Creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
- For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 ULN

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen during the 14 days prior to initiation of study treatment
- Negative HIV test at screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.

- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- Tumor accessible for biopsy
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as outlined for each specific treatment arm in Appendix 7–Appendix 19.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as outlined for each specific treatment arm in Appendix 7–Appendix 19.

4.1.1.3 Inclusion Criteria for Stage 2

Patients must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0–2 (see Appendix 3)
- Patients in the atezolizumab control arm: ability to initiate Stage 2 treatment within 3 months after experiencing loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) while receiving Stage 1 treatment
- Patients in the docetaxel control arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Patients in an atezolizumab-containing experimental arm during Stage 1 with the exception of the atezolizumab plus docetaxel arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) while receiving Stage 1 treatment
- Patients in the atezolizumab plus docetaxel arm: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity related to docetaxel or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or disease progression per RECIST v1.1 while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible by the investigator)

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment during Stage 1 and Stage 2 if they meet any of the applicable criteria outlined in subsequent sections, as summarized by treatment arm in Table 7. If a patient is eligible only for a control arm, the patient will not be enrolled in the study. Event grades in the exclusion criteria are based on NCI CTCAE v4.0.

Table 7 Arm-Specific Exclusion Criteria

Stage	Cohort	Treatment Arm	Applicable Exclusion Criteria
1	1	Atezo	Sections 4.1.2.1 and 4.1.2.2
		Atezo + Cobi	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
	2	Docetaxel	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
		Atezo + Cobi	Sections 4.1.2.1, 4.1.2.2, 4.1.2.3, and 4.1.2.4
		Atezo + Ipat	Sections 4.1.2.1, 4.1.2.2, 4.1.2.4, and 4.1.2.5
		Atezo + Evo	Sections 4.1.2.1 and 4.1.2.2
		Atezo + Docetaxel	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
		Atezo + Bev	Sections 4.1.2.1, 4.1.2.2, 4.1.2.4, and 4.1.2.6
		Atezo + Bev + RTx	Sections 4.1.2.1, 4.1.2.2, 4.1.2.6, and 4.1.2.7
		Atezo + SG	Sections 4.1.2.1, 4.1.2.2
2	1	Atezo + Pem + Carbo	Sections 4.1.2.2 and 4.1.2.8
		Atezo + Gem + Carbo	Sections 4.1.2.2 and 4.1.2.9
	2	Atezo + Docetaxel	Sections 4.1.2.2 and 4.1.2.4
		Atezo + Lina	Sections 4.1.2.2 and 4.1.2.10

Atezo = atezolizumab; Bev = bevacizumab; Carbo = carboplatin; Cobi = cobimetinib; Evo = evolocumab; Gem = gemcitabine; Ipat = ipatasertib; Lina = linagliptin; Pem = pemetrexed; RTx = radiotherapy; SG = sacituzumab govitecan.

4.1.2.1 Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- Activating mutation in the *EGFR* gene or *ALK* gene rearrangement

  Patients with unknown *EGFR* and/or *ALK* status will undergo testing at a local laboratory at screening with the exception of patients with squamous NSCLC.

- Prior treatment with any of the protocol-specified study treatments (including TROP-2-targeting agents), with the following exception:

  Patients in Cohort 2 who received atezolizumab, bevacizumab, pemetrexed, gemcitabine, and/or carboplatin for treatment of NSCLC as well as patients who received evolocumab for an approved indication are eligible for the study.

- Prior treatment with a topoisomerase 1 inhibitor

- For patients in Cohort 2: prior treatment with a T-cell co-stimulating therapy or an immune checkpoint inhibitor other than a PD-L1/PD-1 checkpoint inhibitor and anti–CTLA-4 antibodies

  Patients who discontinued a PD-L1/PD-1 checkpoint inhibitor primarily for toxicity or intolerability are not eligible for the study.

- For patients in Cohort 2: immune checkpoint inhibitor or biologic treatment (e.g., bevacizumab) within 2 weeks prior to initiation of study treatment, or other systemic treatment for NSCLC within 2 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Eligibility only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to the initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor–α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressant medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose, systemic immunosuppressant medications or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Use of an indwelling catheter (e.g., PleurX®) is allowed.
- Uncontrolled tumor-related pain

  Patients requiring pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected serum calcium > ULN)
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases

  Patients with a history of CNS metastases treated with CNS-directed therapies (e.g., stereotactic body radiotherapy [SBRT], whole-brain radiotherapy [WBRT]) are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.
  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  – There is no evidence of interim progression between completion of CNS-directed therapy and the screening brain scan.
  – The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or WBRT within 14 days prior to initiation of study treatment.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- History of leptomeningeal disease
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  - Rash must cover $<10\%$ of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- History of malignancy other than NSCLC within 2 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study

  Placement of central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

- Adverse events from prior anti-cancer therapy that have not resolved to Grade≤ 1 or better, with the exception of alopecia of any grade, Grade ≤ 2 peripheral neuropathy, and immune checkpoint inhibitor-related hypothyroidism Grade ≤ 2

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or their excipients
- Patients entering Stage 2: inability to tolerate atezolizumab during Stage 1
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

4.1.2.3 Additional Exclusion Criteria for Atezo + Cobi Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the Atezo + Cobi arm during Stage 1:

- Prior treatment with mitogen-activated protein kinase (MAPK) inhibitors (including cobimetinib)
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or below 50%, whichever is lower
- Known risk factors for ocular toxicity, consisting of any of the following:
  - History of serous retinopathy
  - History of retinal vein occlusion (RVO)
  - Evidence of ongoing serous retinopathy or RVO at baseline

4.1.2.4 Additional Exclusion Criteria for Docetaxel-Containing Arms during Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from docetaxel-containing arms during Stage 1 and Stage 2:

- Prior treatment with docetaxel
- History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80
- Grade $\geq$ 2 peripheral neuropathy
- Treatment with strong inhibitors or strong inducers of CYP3A4 within 14 days prior to initiation of study treatment or anticipation of need for such treatment during study treatment

4.1.2.5 Additional Exclusion Criteria for Atezo + Ipat Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the ipatasertib-containing arm during Stage 1:

- Prior treatment with ipatasertib or other Akt inhibitors
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceremia
- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication are allowed.

  Diabetic patients with fasting total serum glucose > 8.3 mmol/L (150 mg/dL) and/or $HbA_{1C} > 7.5$ are not eligible for enrollment.
- Congenital long QT syndrome or screening QT interval corrected through use of Fridericia's formula > 480 ms
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, evidence of prior myocardial infarction
- Treatment with strong CYP3A4 inducers or inhibitors within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug, or anticipation of the need for such treatment while on study

4.1.2.6 Additional Exclusion Criteria for Bevacizumab-Containing Arms during Stage 1

Patients who meet any of the following criteria will be excluded from the bevacizumab-containing arms during Stage 1:

- Patients with squamous NSCLC
- Inadequately controlled hypertension (defined as systolic blood pressure [BP] > 150 mmHg and/or diastolic BP > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions

  Anti-hypertensive therapy to achieve these parameters is allowed.
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to initiation of study treatment
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (≤ 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day) or clopidogrel (>75 mg/day)

Note: The use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed. However, the use of direct oral anticoagulant therapies, such as dabigatran (Pradaxa®) and rivaroxaban (Xarelto®), is not recommended due to bleeding risk.

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to initiation of study treatment
- History of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, within 6 months prior to initiation of study treatment or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to initiation of study treatment

  Patients with signs or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.
- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Grade ≥2 proteinuria, as demonstrated by ≥2+ protein on dipstick urinalysis and ≥1.0 g of protein in a 24-hour urine collection

  All patients with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with <2+ protein on dipstick urinalysis are eligible for the study.
- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (<30 mm from the carina) of large volume
- History of intra-abdominal inflammatory process within 6 months prior to initiation of study treatment, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Ablative radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study treatment
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to initiation of study treatment; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study treatment; or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure

4.1.2.7 Additional Exclusion Criteria for Radiotherapy-Containing Arm during Stage 1

Patients who meet any of the following criteria will be excluded from the radiotherapy-containing arm during Stage 1:

- Patients who meet any of the exclusion criteria for bevacizumab-containing arms listed under Section 4.1.2.6
- Lack of lesions where SBRT can safely be applied
- Serious medical comorbidities precluding radiotherapy. These include, but are not limited to, the following:
  - Interstitial lung disease in patients requiring thoracic radiation
  - Active Crohn disease in patients where the GI tract will receive radiotherapy, or active ulcerative colitis where the bowel will receive radiotherapy
  - Connective tissue disorders such as lupus or scleroderma
  - Known genetic disorders associated with increased toxicity to radiation therapy, e.g, ataxia telangiectasia
- Substantial overlap with a previously treated radiation volume:
  - Prior radiotherapy in general is allowed, as long as the composite plan meets dose constraints herein.
  - For patients treated with radiation previously, biological effective dose calculations should be used to equate previous doses to the tolerance doses listed in the technical radiotherapy manual. All such cases must be discussed with the responsible radiotherapy investigator at the site. *The Medical Monitor is available to advise as needed.*
  - Lesions that have been treated with radiotherapy within the last 6 months should not be radiated

4.1.2.8 Additional Exclusion Criteria for Atezo + Pem + Carbo Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Pem + Carbo arm during Stage 2:

- Histologically or cytologically confirmed squamous NSCLC
- History of allergic reaction to carboplatin, other platinum-containing compounds, or pemetrexed
- Creatinine clearance < 45 mL/min (calculated using the Cockcroft-Gault formula)

4.1.2.9 Additional Exclusion Criteria for Atezo + Gem + Carbo Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo + Gem + Carbo arm during Stage 2:

- Histologically or cytologically confirmed non-squamous NSCLC

- History of allergic reaction to carboplatin, other platinum-containing compounds, or gemcitabine
- Creatinine clearance <45 mL/min (calculated using the Cockcroft-Gault formula)
- Radiation therapy within 7 days prior to initiation of gemcitabine

4.1.2.10 Additional Exclusion Criteria for Atezo+ Lina Arm during Stage 2

Patients who meet any of the following criteria will be excluded from the Atezo+Lina arm during Stage 2:

- Known diagnosis of Type 2 diabetes mellitus currently treated with a DPP-4 inhibitor
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through use of the IxRS and will retain the same patient identification number that was assigned in Stage 1.

For Stage 1, this study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment over the course of the study. The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that the likelihood of being allocated to the control arm will be no more than 35%. The randomization ratios may be altered to increase enrollment in a particular arm.

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Sections 4.1.1 and 4.1.2. For example, the Atezo+Cobi arm will be removed as an option for patients who are ineligible for that arm. If a patient is randomized to the Atezo+Bev+RTx arm but cannot start treatment with radiotherapy for clinical/technical reasons (e.g., contraindication for radiotherapy that is detected after randomization, e.g., during the radiotherapy planning process), this patient will be allowed to skip radiotherapy and start treatment with Atezo+Bev. The reason for skipping radiotherapy will be documented accordingly. If a patient is only eligible for a control arm, the patient will not be enrolled in the study.

If more than one mandatory serial biopsy arm is open for enrollment at a time, eligible patients (at participating sites) will be assigned to one of the available arms by the Sponsor.

Assignment to Stage 2 treatment arms will be determined by histologic type (non-squamous vs. squamous) for patients in Cohort 1. Patients in Cohort 2 who are eligible for more than one treatment arm will be assigned a treatment arm by the investigator.

Patients who do not receive at least one dose of each drug for their assigned systemic treatment regimen will not be included in the efficacy analyses. Additional patients may be enrolled in Stage 1 to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4 for Stage 1 and Table 6 for Stage 2.

4.3.1 Investigational Medicinal Product Accountability

The IMPs for this study are atezolizumab, cobimetinib, docetaxel, ipatasertib, pemetrexed, carboplatin, gemcitabine, linagliptin, bevacizumab, sacituzumab govitecan, and evolocumab. All IMPs required for completion of this study will be provided by the Sponsor where required by local practices. The study site will acknowledge receipt of IMPs supplied by the Sponsor. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on a drug inventory log.

4.3.2 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm (see Appendix 7–Appendix 19).

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in Appendix 7–Appendix 19. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each infusion; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Written informed consent must also be obtained before performing screening evaluations and study-related procedures for Stage 2.

Screening evaluations for Stage 1 and Stage 2 are to be performed within 28 days prior to initiation of study treatment (Day 1). For the Atezo+Bev+RTx arm, screening evaluations are to be performed within 28 days prior to randomization . All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment.

Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to Day 1, or, for the Atezo+Bev+RTx arm, within a specified time prior to randomization (see the schedule of activities for screening in Appendix 2) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.
The patient's molecular profile for lung cancer, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all

medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified time prior to initiation of study treatment will be recorded (as outlined for each arm in Appendix 7–Appendix 19). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature.

Vital signs should be measured at specified timepoints, as outlined for each arm in the schedules of activities (see Appendix 7–Appendix 19), and as clinically indicated.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following initiation of treatment and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. However, patients in atezolizumab-containing arms who continue treatment after radiographic disease progression will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and/or evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable but will be documented at screening as a site of metastatic disease. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment, or, for the Atezo + Bev + RTx arm, within 28 days prior to randomization, do not have to be repeated at screening.

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and/or evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluations according to the schedule above. Brain metastases treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). To facilitate evaluation of *post-progression tumor changes while treatment is ongoing*, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression),

and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments.

Overall response at a single timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 1).

Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator prior to treatment administration.

4.5.6 Ophthalmologic Examinations

If a cobimetinib-containing arm is open for enrollment, all patients will undergo ophthalmologic examinations at screening, and patients in arms that require additional ophthalmologic examinations (e.g., Atezo+Cobi arm) will undergo ophthalmologic examinations at specified timepoints during the study. Patients will be evaluated at screening for risk factors for ocular toxicity, including history of serous retinopathy, history of RVO, and evidence of ongoing serous retinopathy or RVO at baseline.

Ophthalmologic examinations will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT). If spectral domain OCT is not available, time-domain OCT may be performed instead. Ophthalmologic examinations must be performed by a qualified ophthalmologist.

4.5.7 Evaluation of Left Ventricular Function

If a cobimetinib-containing arm is open for enrollment, all patients will undergo evaluation of LVEF, either by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan, at screening, and patients in arms that require additional LVEF examinations (e.g., Atezo+Cobi arm) will undergo evaluation of LVEF at specified timepoints during the study and as clinically indicated for new or worsening symptoms. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment as per institutional guidelines. Evaluation of left ventricular function must be performed using the same method for each patient.

Guidelines for management of decreased LVEF are provided in Appendix 8 (Section A8–5.1.4.3).

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, amylase, and lipase in all arms and CPK, GGT, and ferritin in specified arms
- HbA_{1c} and fasting lipid panel (performed for specified arms only; details provided in schedules of activities; only if an ipatasertib-containing [HbA_{1c} and fasting lipid panel] or evolocumab-containing [fasting lipid panel] arm is open for enrolment)
- Coagulation: INR and aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology, unless not permitted per local regulations
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- C-reactive protein
- LDH
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

  For patients on a bevacizumab-containing arm, if urinary protein is $\geq 2+$ on dipstick, then a 24-hour urine collection is required to check the total urinary protein. If there is an explanation for the positive dipstick result (e.g., menses), it should be recorded and there is no need to perform further laboratory assessments.

- Determination of PD-L1 expression through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 (assay not needed for patients with prior result using one of these assays) and *EGFR* and *ALK* status (not needed for patients with known status and patients with squamous NSCLC) through testing performed on tumor tissue collected at baseline

    Baseline tumor tissue samples from the primary lesion or a metastatic lesion will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be used, provided the patient has not received any checkpoint inhibitor therapy since the time of the biopsy. For patients in Cohort 2 who have received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue *may* be discussed with the Medical Monitor.

    A representative FFPE tumor specimen in a paraffin block (preferred) or at least *15*–16 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report to the designated central laboratory, once a patient is randomized.

    Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that requires decalcification is not acceptable.

    Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

Samples for the following laboratory test will be sent to a central laboratory or to the study site's local laboratory for analysis:

- Soluble CD25 (performed for specified arms only; details provided in the respective schedules of activities)

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody in all arms and anti-citrullinated peptide antibody in specified arms only

    The serum autoantibody sample collected at screening will be analyzed only if a patient experiences a suspected immune-mediated adverse event and the

serum autoantibody results are positive during the treatment period. These analyses will be performed using validated assays.

- Plasma or serum samples for PK analysis (see Appendix 7–Appendix 19)
- Plasma or serum samples for immunogenicity analysis (see Appendix 7–Appendix 19)
- Plasma, serum, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers (see Appendix 7–Appendix 19)
- Blood samples for blood-based NGS ctDNA assay for exploratory research on biomarkers (performed for specified arms only; details provided in the respective schedules of activities)
- Tumor tissue sample collected at baseline (as described above) for exploratory research on biomarkers
- Mandatory serial biopsy arms at participating sites (see Section 3.1.2): tumor tissue sample collected 4 weeks (±7 days) after initiation of Stage 1 treatment (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

  Patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥1 cm apart.

  The Informed Consent Form will contain a separate section that addresses the mandatory serial biopsy arms. A separate, specific signature will be required to document a patient's agreement to participate in one of these arms.
- Tumor tissue sample collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) (if deemed clinically feasible by the investigator) for exploratory research on biomarkers

  Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire, carcinoembryonic antigen, or density, localization, and activation status of immune cells and their subsets, and may involve DNA or RNA extraction, analysis of somatic mutations, and use of NGS or WES.

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report,

which is available upon request directly from Foundation Medicine. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has been approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum and plasma samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, PBMC, blood, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of the samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Electrocardiograms

An ECG will be performed at screening, at specified timepoints for arms that require additional ECG monitoring, and as clinically indicated, as outlined for each arm in the

schedules of activities (see Appendix 7–Appendix 19). ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.10 Optional Tumor Biopsies

Patients will be given the option of consenting to additional tumor biopsies. Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation, if deemed clinically feasible. In addition, patients who consent to optional biopsies may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

An Informed Consent Form with a separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.8. Refer to Section 4.5.8 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to CIT or diseases:

- Blood samples collected on Day 1 of Cycle 1 during Stage 1 and Stage 2
- Leftover blood, serum, plasma, PBMC, and tissue samples (with the exception of leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) collected during Stage 1 or Stage 2 of the study, including leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient’s potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient’s safety if he or she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol anti-cancer therapy
- Pregnancy

- Atezolizumab control arm and atezolizumab-containing experimental arms: loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). For details on study treatment discontinuation in the atezolizumab plus docetaxel arm, see Section 3.1.1.
- Docetaxel control arm: radiographic disease progression per RECIST v1.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease or loss of clinical benefit may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities provided for each arm in Appendix 7–Appendix 19.

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

A safety plan for each treatment arm, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided in the respective appendix for that treatment arm (Appendix 7–Appendix 19).

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.3.5.12.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10, for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for each treatment arm are listed in the respective appendix for that treatment arm (see Appendix 7–Appendix 19).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.3.5.12–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 8 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on NCI CTCAE (v4.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 9):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 9 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related or Injection-Site Reactions *and Cytokine-Release Syndrome*

There may be significant overlap in signs and symptoms of infusion-related reactions (IRRs) and cytokine release syndrome (CRS). While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion or injection should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction", "injection-site reaction", *or "cytokine-release syndrome")*. Avoid ambiguous terms such as "systemic reaction." *Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF.* Associated signs and symptoms should be recorded on the dedicated Infusion-Related, Injection Reaction eCRF*, or Cytokine-Release Syndrome eCRF, as appropriate*. If a patient experiences both a local and systemic reaction to *a single administration* of study treatment, each reaction

should be recorded separately on the Adverse Event eCRF, with *associated* signs and symptoms also recorded separately on the dedicated Infusion-Related, Injection Reaction eCRF*, or Cytokine-Release Syndrome eCRF*.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided Appendix 6.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related or injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the

Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of NSCLC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NSCLC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose

- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab (RO5541267), cobimetinib (RO5514041), evolocumab, ipatasertib (RO5532961), linagliptin, docetaxel, sacituzumab govitecan, pemetrexed, carboplatin, gemcitabine, and bevacizumab (RO4876646), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with atezolizumab, cobimetinib, evolocumab, ipatasertib, linagliptin, docetaxel, sacituzumab govitecan, pemetrexed, carboplatin, gemcitabine, and bevacizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report

such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Primary Medical Monitor/ Roche Medical Responsible:	Jan Pintoffl, M.D.
Email:	jan.pintoffl@roche.com
Telephone No.:	+41 61 687 05 81
Mobile Telephone No.:	+41 79 563 72 75
Backup Medical Monitor:	Nedal Al-Sakaff
Email:	nedal.al-sakaff@roche.com
Telephone No.:	+41 61 688 17 43
Mobile Telephone No.:	+41 79 618 76 02

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day,

7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special *Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special *Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$ 135 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

Reporting requirements for pregnancies are described for each treatment arm in the respective appendix for that treatment arm (see Appendix 7–Appendix 19).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 135 days after the last dose of study treatment or until initiation of new, non–protocol-specified systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Atezolizumab Investigator's Brochure
- Cobimetinib Investigator's Brochure
- Ipatasertib Investigator's Brochure

- Bevacizumab Investigator's Brochure
- Sacituzumab Govitecan Investigator's Brochure
- Summary of Product Characteristics for carboplatin, docetaxel, evolocumab, gemcitabine, linagliptin, and pemetrexed

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and other analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually received, and as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and minimum and maximum values. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

New baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.5. For other endpoints (e.g., change from baseline in vital signs or laboratory test results), the last non-missing value prior to the patient's first dose during Stage 2 will serve as the new baseline.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with metastatic NSCLC.

Approximately 255–435 patients will be randomly allocated to the control and experimental arms during the study.

Approximately 15 patients with serial biopsy samples will be enrolled in each mandatory serial biopsy arm.

However, the number of patients may be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to approximately 15 patients per CIT combination within each cohort.

With approximately 15 patients with serial biopsies in each arm, an 80% two-sided confidence interval for a 30% increase in $CD8^+$ T cells in the center of the tumor would be 22.8%, 37.2%, assuming a standard deviation of 0.20 for the difference in $CD8^+$T cells between paired samples (i.e., baseline vs. on-treatment samples, baseline vs. post-progression samples, or on-treatment vs. post-progression samples).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm within the two stages. Patient disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm within each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm within each stage, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. Reasons for discontinuation of study drugs will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, histology [squamous vs. non-squamous], and baseline ECOG Performance Status) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response during Stage 1, as defined in Section 2 (see Table 2). Patients with missing or no response assessments will be classified as non-responders.

ORR, defined as the proportion of patients with a complete or partial response, will be calculated for each arm, along with 95% confidence intervals (Clopper–Pearson method). The difference in ORR between the experimental arms and the corresponding control arm will also be calculated, along with 95% confidence intervals.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, OS, OS at specific timepoints (e.g., 6 months), duration of response (DOR), and disease control during Stage 1, as defined in Section 2 (see Table 2). PFS, DOR, and disease control are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a complete or partial response.

For patients who do not have documented disease progression or death in a study stage, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% confidence intervals constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated through use of the Kaplan-Meier method, with 95% confidence intervals calculated on the basis of the Greenwood estimate for the variance.

Disease control rate, defined as the proportion of patients with stable disease for $\geq$ 12 weeks, a partial response, or a complete response, will be calculated for each treatment arm, with 95% confidence intervals estimated through use of the Clopper-Pearson exact method.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are objective response, PFS, DOR, and disease control during Stage 2, as determined by the investigator according to RECIST v1.1 (see Table 3).

Objective response, PFS, DOR, and disease control will be analyzed through use of the same methods described in Sections 6.4.1 and 6.4.2. DOR will be derived for efficacy-evaluable patients with a complete or partial response.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm within each stage.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade ≥ 3 adverse events, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for potential PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and specified drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) by treatment arm, and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. PK data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity may be assessed for atezolizumab and other study treatments as appropriate (refer to arm-specific appendices for details). The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or are missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer units

greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be post-treatment-ADA negative if they are ADA negative or are missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer units greater than the titer of the baseline sample (treatment unaffected).

For other study treatments where ADA is tested, positivity will be determined according to standard methods established in previous studies of that drug.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints.

6.9 INTERIM ANALYSES

It is anticipated that interim analyses will be conducted over the course of the study, with the earliest (Stage 1) interim analysis taking place when at least one experimental arm has completed enrollment in the preliminary phase, approximately 15 patients have been enrolled in the control arm for that same cohort, and patients have been followed for a minimum of 6 weeks for the primary endpoint analysis (ORR). If no complete or partial responses are observed in an experimental arm, enrollment in that arm will be stopped. Otherwise, a posterior probability may be used to guide further enrollment in a treatment arm based on an interim analysis of clinical activity in the experimental arm compared with the control arm.

If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be further enrollment of 25 additional patients in the experimental arm.

If enrollment in the Atezo + Docetaxel arm is stopped in Stage 1 on the basis of the interim analysis, enrollment in the Atezo + Docetaxel arm in Stage 2 will be paused to allow for further evaluation.

An interim analysis will also be conducted after approximately 15 patients have been enrolled in a Stage 2 treatment arm and followed for a minimum of 6 weeks. If no complete or partial responses are observed after at least 15 patients have been enrolled and followed for a minimum of 6 weeks in the Atezo + Pem + Carbo arm, the Atezo + Gem + Carbo arm, the Atezo + Lina arm, or the Atezo + Docetaxel arm (Stage 2), further enrollment in that arm will be stopped.

The interim analyses will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate

and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, they will be provided in a certified translation into the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and

IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area (e.g., brain metastases) or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new

lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedules of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCE

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 2
Schedules of Activities for Screening

Table 1 Schedule of Activities for Stage 1 Screening

Assessment/Procedure	Stage 1 Screening [a] (Day –28 to –1)
Informed consent	x [b]
Demographic data	x
Medical history and baseline conditions	x
Molecular profile of lung cancer (if available)	x
Vital signs [c]	x
Weight	x
Height	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
ECHO or MUGA scan [f]	x
Ophthalmologic examination [g]	x
Hematology [h]	x [i]
Chemistry [j, k]	x [i]
Amylase, lipase, fasting lipid panel [l]	x [i]
HbA_{1c} [m]	x
Coagulation (INR, aPTT)	x [i]
TSH, free T3 (or total T3 [n]), free T4	x
Viral serology [o]	x
C-reactive protein	x
LDH	x [i]
Pregnancy test [p]	x [i]
Urinalysis [q]	x
Serum autoantibody sample [r]	x
Blood sample for blood-based NGS ctDNA test [s]	x
Tumor biopsy [t]	x
Baseline tumor assessments [u, v]	x [i]
Concomitant medications [w]	x
Adverse events [x]	x

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy; CPI = checkpoint inhibitor; CT = computed tomography; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; ECHO=echocardiogram; eCRF = electronic Case Report Form; FDG = fluorodeoxyglucose; HbA1c = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MUGA=multiple-gated acquisition;

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

NGS = next-generation sequencing; PET = positron emission tomography; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within a specified time prior to randomization may be used; such tests do not need to be repeated for screening or re-screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[c] Includes respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[e] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] ECHO or MUGA scan will be performed only if a cobimetinib-containing arm is open for enrollment.

[g] Clinical history of ophthalmologic risk factors (i.e., history of neurosensory retinal detachment, RVO, or neovascular macular degeneration) will be evaluated only if a cobimetinib-containing arm is open for enrollment. Patients who are allocated to a cobimetinib-containing arm will undergo ophthalmologic examinations prior to Day 1 of Cycle 1 (see Table 5 in Appendix 8, Section A8–6).

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1). For the Atezo + Bev + RTx arm, screening laboratory test results must be obtained within 14 days prior to randomization.

[j] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[k] A fasting chemistry panel (performed after ≥ 8 hr of fasting) is required if an ipatasertib-containing arm is open for enrollment; otherwise, a fasting chemistry panel is not required.

[l] Fasting lipid panel (consisting of cholesterol, HDL, LDL, and triglyceride) will be assessed (after ≥ 8 hr of fasting) only if an ipatasertib- or an evolocumab-containing arm is open for enrollment.

[m] HbA_{1c} will be assessed (after ≥ 8 hr of fasting) only if an ipatasertib-containing arm is open for enrollment.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4.

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

[o] Patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HbsAb, total HbcAb, and HCV antibody. If a patient has a negative HbsAg test and a positive total HbcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[p] All women of childbearing potential will have a serum pregnancy test at screening.

[q] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Patients with non-squamous NSCLC with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein, but only if a bevacizumab-containing arm is open for enrollment.

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[s] Blood-based NGS ctDNA assay will be used to assess molecular alterations associated with CPI resistance. Turnaround time for the blood-based NGS ctDNA assay is approximately 14 calendar days upon receipt of the blood samples at the testing laboratory.

[t] Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. For patients in Cohort 2 who received treatment with checkpoint inhibitor therapy beyond initial radiographic progression per RECIST v1.1, collection of tumor tissue *may* be discussed with the Medical Monitor. Refer to Section 4.5.8 for tissue sample requirements.

[u] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment, or within 28 days prior to randomization for the Atezo+Bev+RTx arm, do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[v] For patients that are potentially eligible for radiotherapy-containing arm, pretreatment 18-FDG PET/CT imaging is strongly recommended. 18-FDG PET/CT imaging performed as standard of care prior to obtaining information consent and within 56 days prior to randomization do not need to be repeated at screening.

Table 1 Schedule of Activities for Stage 1 Screening (cont.)

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 7 days prior to initiation of study treatment.

[x] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Table 2 Schedule of Activities for Stage 2 Screening

Assessment/Procedure	Stage 2 Screening [a]
Informed consent	x [b]
Molecular profile of lung cancer (if available)	x
Vital signs [c]	x
Weight	x
Complete physical examination [d]	x
ECOG Performance Status	x
ECG [e]	x
Hematology [f]	x [g]
Chemistry [h]	x [g]
Coagulation (INR, aPTT)	x [g]
TSH, free T3 (or total T3 [i]), free T4	x
Viral serology [j]	x
Pregnancy test [k]	x [g]
Urinalysis [l]	x [g]
Blood sample for blood-based NGS ctDNA test [m]	x
C-reactive protein	x
LDH	x [g]
Tumor response assessments [n]	x [n, o]
Concomitant medications [p]	x
Adverse events [q]	x

CPI = checkpoint inhibitor; CT = computed tomography; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FDG = fluorodeoxyglucose; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PET = positron emission tomography; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] The visit at which response assessment shows progressive disease may be used as the Stage 2 screening visit. Patients who fail their first screening for study eligibility may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening.

[b] Written informed consent must be obtained before performing screening evaluations for Stage 2 except as noted in footnote "o" below.

[c] Includes respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic

Table 2 Schedule of Activities for Stage 2 Screening (cont.)

systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[e] Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[f] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[g] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), CPK, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST.

[i] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4.

[j] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[k] All women of childbearing potential will have a serum pregnancy test.

[l] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[m] For patients who did not have a blood sample collected at the Stage 1 treatment discontinuation visit, a sample will be collected for the blood-based NGS ctDNA assay, which will be used to assess potential changes in molecular alterations associated with CPI resistance. Turnaround time for the blood-based NGS ctDNA assay is approximately 14 calendar days upon receipt of the blood samples at the testing laboratory.

[n] All measurable and evaluable lesions should be assessed and documented. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). Bone scans and CT scans of the neck should be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[o] Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

[p] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 10 days prior to initiation of study treatment.

Table 2 Schedule of Activities for Stage 2 Screening (cont.)

[q] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

Appendix 3
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Appendix 4
Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. The Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 5
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 6
Risks Associated with Atezolizumab and Management of Atezolizumab-Specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance for a given patient prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator. The Medical Monitor *is available to advise as needed*.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day *IV methylprednisolone*. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed*.

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • *Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.* • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2-4	• Permanently discontinue atezolizumab and contact Medical Monitor.[a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor [e]. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*. For subsequent infusions, administer oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and documented by* the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist*. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients

with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

Table 12 Management Guidelines for Renal Events (cont.)

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥38.5°C

- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL) ($<$ 100 g/L [10 g/dL] for infants $<$ 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble IL-2 receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq 181 \times 10^9$/L (181,000/μL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 7
Study Details Specific to Atezo Arm (Control for Cohort 1)

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A7–1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A7–2 RATIONALE FOR ATEZO ARM

A7–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer.

PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A7–2.2 BENEFIT–RISK ASSESSMENT

Atezolizumab will be the control arm for Cohort 1, which consists of patients with high tumor PD-L1 expression (tumor proportion score [TPS] $\geq$50%, as determined through use of the Dako PD-L1 IHC 22C3 pharmDx assay or the Ventana PD-L1 IHC SP263 assay) who have received no prior systemic therapy for metastatic NSCLC.

Pembrolizumab, a PD-1 inhibitor (and current standard of care in this patient population), and atezolizumab, a PD-L1 inhibitor, target the same immune evasion mechanism. Reported clinical data suggest that both drugs confer comparable survival benefit and have a similar safety profile in a patient population that expresses high levels of PD-L1.

Both pembrolizumab and atezolizumab have demonstrated superiority over docetaxel by further extending median survival in patients with metastatic NSCLC who experienced disease progression during or following platinum-containing chemotherapy. While pembrolizumab approval is restricted to patients whose tumors express PD-L1, atezolizumab approval is not restricted on the basis of PD-L1 expression. However, the two drugs appear to confer comparable survival benefit in previously treated patients with $\geq$50% PD-L1 expression on tumors (TPS $\geq$50% for pembrolizumab and TC3/IC3 for

atezolizumab). In this population, the median overall survival (OS) was 17.3 months versus 8.2 months for pembrolizumab and docetaxel, respectively, and 20.5 months versus 8.9 months for atezolizumab and docetaxel, respectively (Garon et al. 2015; Rittmeyer et al. 2017). The objective response rate (ORR), 44% for pembrolizumab and 31% for atezolizumab, was also comparable in this population (Garon et al. 2015; Rittmeyer et al. 2017).

Pembrolizumab was also granted approval in previously untreated patients with $>$50% PD-L1 expression on tumors on the basis of increased survival benefit compared with platinum-based chemotherapy. Notably, in this population, the OS rate at 12 months in pembrolizumab-treated patients was comparable to that in atezolizumab-treated patients (70% for pembrolizumab and 61.5% for atezolizumab) (Reck et al. 2016; Garassino et al. 2017). An updated survival analysis from Study GO28754 (BIRCH), with a minimum follow-up of 20 months, showed a median OS of 26.9 months in previously untreated patients with high PD-L1 expression (TC3/IC3), which compares favorably with historical data with combination chemotherapy (Garassino et al. 2017). The ORR in this population was comparable for pembrolizumab (45%) and atezolizumab (34%) and in both cases was slightly higher than that in previously treated patients.

Based on the totality of evidence described above, atezolizumab is considered to be an appropriate treatment option for previously untreated NSCLC patients whose tumors express high levels of PD-L1.

For evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A7–3 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A7–4 MATERIALS AND METHODS SPECIFIC TO ATEZO ARM

A7–4.1 TREATMENT IN ATEZO ARM

A7–4.1.1 Formulation, Packaging, and Handling

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A7–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab (Atezo) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after treatment randomization.

Table 1 Treatment Regimen for Atezo Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle

Atezo = atezolizumab.

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5 . Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A7–5.1.2. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available to date.

A7–4.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) will be given the option of receiving a different treatment

combination during Stage 2, as outlined in Table 3, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo Arm

Histologic Type	Study Treatment	Appendix
Non-squamous	Atezo + Pem + Carbo	Appendix 14
Squamous	Atezo + Gem + Carbo	Appendix 15

Atezo = atezolizumab; Carbo = carboplatin; Gem = gemcitabine; Pem = pemetrexed.

Refer to Appendix 14 and Appendix 15 for details specific to the atezolizumab plus pemetrexed plus carboplatin arm and atezolizumab plus gemcitabine plus carboplatin arm, respectively.

A7–4.2 CONCOMITANT THERAPY FOR ATEZO ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A7–4.2.1 Permitted Therapy for Atezo Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A7–4.2.3).

- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.
  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A7–4.2.2 and A7–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A7–4.2.2 Cautionary Therapy for Atezo Arm

A7–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to for details).

A7–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A7–4.2.3) may be used during the study at the discretion of the investigator.

A7–4.2.3 Prohibited Therapy for Atezo Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A7–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A7–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO ARM

Contraception requirements for women in the Atezo arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A7–5 ASSESSMENT OF SAFETY FOR ATEZO ARM

A7–5.1 SAFETY PLAN FOR ATEZO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A7–5.1.1 and A7–5.1.2). Guidelines for management of patients who experience specific adverse events are provided in Appendix 6 .

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A7–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A7–5.1.2 Management of Patients Who Experience Specific Adverse Events in Atezo Arm

A7–5.1.2.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

A7–5.1.2.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A7–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A7–5.1.2.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.*

A7–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A7–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO ARM

A7–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue atezolizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A7–5.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A7–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A7–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO ARM

Table 4 Schedule of Activities for Atezo Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available				
Vital signs [e]		x	x	x	x	
Weight [f]		x		x	x	
Complete physical examination [g]					x	
Limited physical examination [f, h]		x	x	x		
ECOG Performance Status [f]		x		x	x	
ECG [f, i]		Perform as clinically indicated				
Hematology [j]		x [k]	x	x	x	
Chemistry [l]		x [k]	x	x	x	
TSH, free T3 (or total T3), and free T4 [m]		x [k]			x	
Pregnancy test [n]		x		x	x	
Urinalysis [o]		Perform as clinically indicated				
Serum autoantibody sample [p]		Perform if a patient experiences a suspected immune-mediated adverse event				
PK samples		Refer to Table 5				
ADA samples		Refer to Table 5				
Biomarker samples		Refer to Table 5				
Blood sample for RBR (optional) [q]		x				

Table 4 Schedule of Activities for Atezo Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2		
	Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months (±7 days)
Tumor biopsy	See Appendix 2	x [r]				
Tumor biopsy (optional)		x [s]				
Tumor response assessments		x [t, u, v]				
Concomitant medications [w]		x	x	x	x	
Adverse events [x]		x	x	x	x [x]	x
Atezolizumab administration [y, z]		x		x		
Survival follow-up and anti-cancer treatment						x [aa]

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; MUGA = multiple-gated acquisition; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

Table 4 Schedule of Activities for Atezo Arm (cont.)

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

Table 4 Schedule of Activities for Atezo Arm (cont.)

[n] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[p] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[q] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[r] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[s] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[t] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[u] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[v] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Table 4 Schedule of Activities for Atezo Arm (cont.)

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[x] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[y] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[z] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[aa] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Table 5: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	At visit	• Biomarker (plasma, serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (± 30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a]

ADA = anti-drug antibody; Atezo = atezolizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Not performed for patients who enter Stage 2.

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Appendix 8
Study Details Specific to Atezo+Cobi Arm

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A8–1 BACKGROUND ON ATEZO + COBI ARM

A8–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as cluster of differentiation [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A8–1.2 BACKGROUND ON COBIMETINIB

Cobimetinib is a potent and highly selective small-molecule inhibitor of MEK1 and MEK2, central components of the MAPK pathway. The MAPK pathway plays a major role in mediating cell growth and differentiation in response to numerous extracellular signals. Activated MEK triggers downstream signaling through ERK to promote growth.

Cobimetinib shows anti-tumor activity in both nonclinical models and patients with cancer and is being studied in combination with several anti-neoplastic agents in various tumor types.

Cobimetinib has been generally well tolerated, and adverse events have been manageable. Common adverse reactions for cobimetinib include diarrhea, nausea, pyrexia, and vomiting.

Cobimetinib is approved in more than 10 countries including the United States and European Union for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, in combination with vemurafenib.

Refer to the Cobimetinib Investigator's Brochure for details on nonclinical and clinical studies.

A8–2 RATIONALE FOR ATEZO + COBI ARM

A8–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head

and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A8–2.2 THE MAPK SIGNALING PATHWAY AND REGULATION OF THE IMMUNE TUMOR MICROENVIRONMENT

The MAPK signaling cascade is a key intracellular signaling network that transduces multiple proliferative and differentiating signals from the extracellular environment to the nucleus of cells to activate cellular growth and differentiation. Signaling through ERK is one major MAPK pathway that has been identified that plays a significant role in normal cellular regulation (Johnson and Lapadat 2002; Roberts and Der 2007). Given the central role that the MAPK pathway plays in normal cellular development, abnormal regulation of this signaling pathway could lead to tumorigenesis through contribution to uncontrolled proliferation, invasion, metastasis, and angiogenesis as well as diminished apoptosis.

The MAPK pathway has also been implicated in the regulation of the immune microenvironment of tumors. In in vitro cell lines, blocking the MAPK pathway was shown to increase antigen expression and enhance reactivity to antigen-specific T lymphocytes (Boni et al. 2010). In melanoma patients who are treated with a BRAF inhibitor and MEK inhibitor, increased intratumoral lymphocytes ($CD4^+$ and $CD8^+$ T cells) were observed compared with those seen prior to treatment (Kakavand et al. 2015). The inhibition of the MAPK pathway leads to an increase in immune effector cells in the tumor, thus priming the microenvironment to enable to immune system to attack the tumor.

Inhibition of the MAPK pathway has focused on the suppression of targets within this signaling network, such as MEK1 and MEK2. There are multiple upstream activating signals, but multiple alternative pathways exist to bypass their inhibition and still activate ERK1 and ERK2. ERK1 and ERK2 can only be activated and phosphorylated by MEK1 and MEK2, which therefore render MEK1 and MEK2 as key signaling hubs for the inhibition of the MAPK pathway.

A8–2.3 COMBINED INHIBITION OF PD-L1 AND MAPK SIGNALING PATHWAYS AS POTENTIAL ANTI-CANCER THERAPY

One potential mechanism for converting otherwise resistant cancers is to recruit immune cells to the tumor sites so that an anti–PD-L1 agent can be effective in activating the local immune system against the cancer cells.

Nonclinical models suggest that MEK inhibition may have pleiotropic effects that could impact the tumor immune microenvironment, as the MAPK pathway has been implicated in the immune resistance of tumors and inhibition of this pathway can lead to increased $CD8^+$ T-cell infiltration (Kakavand et al. 2015; Liu et al. 2015).

Within the tumor, MEK inhibition results in increased major histocompatibility complex class I (MHC-I) expression and tumor antigen presentation, which acts to enhance tumor recognition by the immune system. Interestingly, MEK inhibition in tumors also increases expression of the checkpoint receptor PD-L1, which could counteract the increased presentation of tumor antigens. MEK inhibition may modulate the tumor microenvironment in ways that could enable an improved immune reaction against the tumor. These effects include increased recruitment and activation status of $CD8^+$ and $CD4^+$ T cells, increased tumor antigen presentation, and reduced secretion of granulocyte colony-stimulating factor with reduced mobilization and activity of $CD11^+GRL^+$ myeloid–derived suppressor cells (Phan et al. 2013; Liu et al. 2015; Ebert et al. 2016; Loi et al. 2016), as well as reduced expression of angiogenesis factors with altered tumor vascular support (Ciuffreda et al. 2009; Chang et al. 2013; Mohan et al. 2015). These data suggest that MEK inhibition can modulate the tumor immune microenvironment and enable better tumor recognition and killing by the immune system, particularly when paired with an inhibitor of the PD-L1 pathway.

Upregulation of the MAPK pathway occurs frequently in human cancers, including a high percentage of pancreatic, colon, lung, ovarian, breast, and kidney tumors (Hoshino et al. 1999). Diverse mechanisms can result in aberrant activation, including amplification or gain-of-function mutations in receptor tyrosine kinases or inappropriate autocrine or paracrine signaling through growth factor receptors. For example, the MAPK pathway can be activated by specific mutations in the *KRAS*, *NRAS*, and *BRAF* oncogenes. Oncogenic *KRAS* mutations are found with high incidence in NSCLC (30%; Kempf et al. 2016).

A8–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB AND COBIMETINIB

Study GP28363 is a Phase Ib study of the safety and pharmacology of atezolizumab administered with cobimetinib to patients with locally advanced or metastatic solid tumors. As of 17 January 2017, there were 150 safety-evaluable patients with tumor types, including colorectal cancer, metastatic melanoma, and NSCLC who were receiving different treatment regimens of atezolizumab + cobimetinib.

Overall, 148 patients (98.7%) experienced an adverse event. The most frequently observed adverse events (≥ 30%) were diarrhea (70.7%), fatigue (56.0%), rash (48.0%), vomiting (42.0%), nausea (36.0%), pruritus (35.3%), decreased appetite (34.7%), and constipation (29.3%).

Grade 3 and 4 adverse events were observed in 96 patients (64%), and the most common (≥2.7% or 4 or more patients) included fatigue (10.0%), anemia (9.3%), diarrhea (8.0%), abdominal pain (5.3%), rash, and increased blood CPK (4.7% each), dyspnea and increased AST (4.0% each), increased amylase and hypertension (3.3% each), and ascites, vomiting, peripheral edema, asthenia, pleural effusion, pulmonary embolism, increased blood bilirubin, decreased neutrophil count, and hypophosphatemia (2.7% each).

Seven patients (4.0%) were reported to have had Grade 5 adverse events. The following events led to death in 7 patients (4.7%): pneumonia, large intestine perforation, small intestinal perforation, sepsis, road traffic accident, and respiratory failure.

Sixty-seven safety-evaluable patients (44.7%) had a serious adverse event, most of which were single reports. The exceptions were pneumonia (6%), pyrexia (4%), abdominal pain and dyspnea (3.3% each), vomiting (2.7%), sepsis and pulmonary embolism (2% each), and bacteremia, cellulitis, lung infection, ascites, intestinal obstruction, nausea, fatigue, peripheral edema, pain, pleural effusion, pneumonitis, dehydration, and fall (1.3% each).

All 20 patients with NSCLC experienced an adverse event, 14 patients (70%) experienced a Grade 3 or 4 adverse event (70%), and 11 patients (55%) experienced a serious adverse event.

These findings are consistent with the known adverse event profiles for atezolizumab and cobimetinib and did not represent additive toxicity.

Detailed clinical study results for atezolizumab and cobimetinib can be found in the Atezolizumab Investigator's Brochure and the Cobimetinib Investigator's Brochure, respectively.

A8–2.5 BENEFIT–RISK ASSESSMENT

Taking into account the efficacy data in patients with mCRC, the manageable and tolerable safety profile, and the supportive biomarker data in Study GP28363, atezolizumab plus cobimetinib appears to have promising therapeutic potential in solid tumors such as NSCLC, in which MAPK pathway upregulation can potentially lead to immune resistance.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.4.

A8–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + COBI ARM

A8–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A8–3.2 RATIONALE FOR COBIMETINIB DOSE AND SCHEDULE

In this study, cobimetinib 60 mg will be administered orally once daily (QD) on Days 1–21 of each 28-day cycle. This is the current approved dosage for cobimetinib.

A8–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + COBI ARM

A8–4.1 TREATMENT IN ATEZO + COBI ARM

A8–4.1.1 Formulation, Packaging, and Handling

A8–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A8–4.1.1.2 Cobimetinib

Cobimetinib will be supplied by the Sponsor as 20-mg, film-coated tablets packaged in blister packs (21 tablets per pack; 3 packs per box) for oral administration.

For information on the formulation and handling of cobimetinib, see the pharmacy manual and the Cobimetinib Investigator's Brochure.

A8–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus cobimetinib (Atezo + Cobi) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined

by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + Cobi Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Cobimetinib 60 mg by mouth once daily on Days 1–21 • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Cobi = atezolizumab plus cobimetinib.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab and cobimetinib are available to date.

A8–4.1.2.1 Cobimetinib Administration

Patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally QD on Days 1–21 of each 28-day cycle. At least 7 days off cobimetinib are required prior to starting a new treatment cycle. Cobimetinib should be taken at approximately the same time each day, and no later than 12 hours after the scheduled time. On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel. Cobimetinib may be taken with or without a meal. Cobimetinib should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. If a dose of cobimetinib is missed (i.e., not taken within 12 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

To assess patient compliance with self-administration of cobimetinib, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

Guidelines for cobimetinib dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A8–5.1.4. Cobimetinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the*

duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed. The Medical Monitor *may* be consulted for any major surgery (e.g., involving a body cavity). Cobimetinib should generally be withheld for 2 days prior to the procedure and for 2 weeks afterwards.

A8–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5 . Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A8–5.1.4. Atezolizumab treatment may be suspended for reasons other than

toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A8–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to cobimetinib will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 3, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + Cobi Arm

Cohort	Histologic Type	Study Treatment	Appendix
1	Non-squamous	Atezo + Pem + Carbo	Appendix 14
	Squamous	Atezo + Gem + Carbo	Appendix 15
2	Non-squamous or squamous	Atezo + Docetaxel	Appendix 16
		Atezo + Lina	Appendix 17

Atezo = atezolizumab; Carbo = carboplatin; Cobi = cobimetinib; Gem = gemcitabine; Lina = linagliptin; Pem = pemetrexed.

Refer to Appendix 14, Appendix 15, Appendix 16, and Appendix 17 for details specific to the atezolizumab plus pemetrexed plus carboplatin arm, atezolizumab plus gemcitabine plus carboplatin arm, atezolizumab plus docetaxel arm, and atezolizumab plus linagliptin arm, respectively.

A8–4.2 CONCOMITANT THERAPY FOR ATEZO + COBI ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A8–4.2.1 Permitted Therapy for Atezo + Cobi Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A8–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and cobimetinib may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

Anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to the first doses of study treatment. However, at the discretion of the investigator, anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A8–4.2.2 and A8–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A8–4.2.2 Cautionary Therapy for Atezo + Cobi Arm

A8–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered,

alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The* Medical Monitor *is available to advise as needed*.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A8–4.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Use of strong CYP3A inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) is not recommended during cobimetinib treatment because cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).

Use of strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) is not recommended during cobimetinib treatment because they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

Caution should be exercised when cobimetinib is co-administered with moderate CYP3A inducers and inhibitors.

The above-mentioned cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor *is available to advise* if questions arise regarding medications not listed above.

A8–4.2.2.3 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A8–4.2.3) may be used during the study at the discretion of the investigator.

A8–4.2.2.4 Anticoagulation Therapy

Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin) should be used with caution because of the risk of hemorrhage events with cobimetinib.

A8–4.2.3 Prohibited Therapy for Atezo + Cobi Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A8–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A8–4.3 PROHIBITED FOOD FOR ATEZO + COBI ARM

Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of study treatment.

A8–4.4 CONTRACEPTION REQUIREMENTS FOR ATEZO + COBI ARM

Contraception requirements for women and men in the Atezo + Cobi arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 1 month after the last dose of cobimetinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A8–5 ASSESSMENT OF SAFETY FOR ATEZO + COBI ARM

A8–5.1 SAFETY PLAN FOR ATEZO + COBI ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and cobimetinib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A8–5.1.1, A8–5.1.2, and A8–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A8–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A8–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6

of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A8–5.1.2 Risks Associated with Cobimetinib

The following adverse events are classified as identified risks associated with cobimetinib: severe hemorrhage, serous retinopathy, left ventricular dysfunction, pneumonitis, rhabdomyolysis, and CPK elevations. The following adverse events are classified as potential risks for cobimetinib: severe hepatotoxicity (Grade ≥ 3), impaired female fertility, and teratogenicity and developmental toxicity. In addition, there is the possibility of drug-drug interactions in patients treated with cobimetinib, as described within this appendix (see Section A8–4.2.2.2). Refer to Section 6 of the Cobimetinib Investigator's Brochure for a detailed description of all anticipated risks for cobimetinib.

A8–5.1.2.1 Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK inhibitors, including cobimetinib (Flaherty et al. 2012). Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to evaluate for risk factors for neurosensory retinal detachment. Patients will also undergo complete ophthalmologic examinations at specified timepoints throughout the study and as clinically indicated if a patient notes any visual disturbances. Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.6.

A8–5.1.2.2 Left Ventricular Dysfunction

Decrease from baseline in left ventricular ejection fraction (LVEF) has been reported in patients receiving cobimetinib. Decreased LVEF may be symptomatic or asymptomatic.

All patients will undergo evaluation of LVEF, either by echocardiography or multiple-gated acquisition scan at baseline, at specified timepoints during treatment, at the end of treatment, and as clinically indicated.

A8–5.1.2.3 Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were reported as non-serious and a lower severity (grade).

A8–5.1.2.4 Creatine Phosphokinase Elevations and Rhabdomyolysis

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. Most reported CPK elevations were asymptomatic, non-serious, and resolved with or without study drug

interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141, and rhabdomyolysis has been reported in postmarketing experience. CPK will be monitored at baseline and monthly during treatment or as clinically indicated.

A8–5.1.2.5 Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria have been reported.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients who use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

A8–5.1.2.6 Severe Hepatotoxicity (Grade ≥ 3)

Liver laboratory test abnormalities, including increases in ALT, AST, and ALP, have been reported as adverse events and serious adverse events in patients treated with cobimetinib and vemurafenib. Generally, elevations in liver laboratory tests have been managed effectively with dose modifications.

A8–5.1.2.7 Impaired Female Fertility

Results from nonclinical studies indicate that there is a potential for effects on female fertility. While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes were observed in reproductive tissues of dogs. These changes were reversible upon discontinuation of cobimetinib.

A8–5.1.2.8 Teratogenicity and Developmental Toxicity

There are no data regarding the use of cobimetinib in pregnant women. When cobimetinib was administered to pregnant rats, cobimetinib caused embryolethality and fetal malformations of the great vessels and skull at similar systemic exposures to those observed in patients administered the 60-mg dose. Therefore, teratogenicity and developmental toxicity is a potential risk for cobimetinib, and cobimetinib use is not recommended during pregnancy.

A8–5.1.3 Risks Associated with Combination Use of Atezolizumab and Cobimetinib

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and cobimetinib: hepatic, gastrointestinal, ocular, dermatologic, and pulmonary events.

A8–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Cobi Arm

A8–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of cobimetinib can be reduced by 20 mg once a day (one dose level) decrements up to two times for management of drug-related toxicities (i.e., from 60 to 40 mg and then from 40 to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab at the investigator's discretion. After dose reduction, the dose of cobimetinib may be escalated by a maximum of one dose level (i.e., increase of 20 mg, from 20 to 40 mg or from 40 to 60 mg) at the investigator's discretion, provided there are no safety concerns.

A8–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 4). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Cobimetinib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table 4). If cobimetinib has been withheld for > 28 days because of toxicity, the patient should be discontinued from cobimetinib. However, if the investigator believes the patient is likely to derive clinical benefit, cobimetinib can be resumed after being withheld for > 28 days.

If atezolizumab is discontinued, cobimetinib should also be discontinued. If cobimetinib is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A8–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A8–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 4. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and cobimetinib.
Gastrointestinal toxicity	
General guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. • Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: Medication – Initiate loperamide (4 mg) every 6 hours around the clock, alternating with diphenoxylate hydrochloride (5 mg)/atropine sulfate (0.5 mg) every 6 hours around the clock, until no loose stools for 24 hours. – If Grade ≥2 diarrhea persists after 48 hours of treatment with loperamide and diphenoxylate/atropine, consider initiating second-line agents (e.g., octreotide, budesonide, tincture of opium). Oral Supplementation – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥1 diarrhea or vomiting. Dietary Modifications – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade®).

Atezo + Cobi = atezolizumab plus cobimetinib; CRP = C-reactive protein; *CRS = cytokine-release syndrome;* IRR = infusion-related reaction.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib; *CRS = cytokine-release syndrome;* GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *The Medical Monitor is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.

Atezo + Cobi = atezolizumab plus cobimetinib; *CRS = cytokine-release syndrome;* GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib; *CRS = cytokine-release syndrome;* GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib; *CRS = cytokine-release syndrome;* GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Atezo + Cobi = atezolizumab plus cobimetinib; *CRS = cytokine-release syndrome;* GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. **Acneiform rash:** • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 2 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. **Acneiform rash:** • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) when restarting cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Withhold cobimetinib. • If event resolves to Grade 1 or better, resume cobimetinib. • Permanently discontinue cobimetinib if withheld for > 28 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab and cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib; LFT = liver function test; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and cobimetinib. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-mediated events of > 5 days' duration:** • Consider withholding atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c]

Atezo + Cobi = atezolizumab plus cobimetinib; LFT = liver function test; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and cobimetinib. • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c]
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.

Atezo + Cobi = atezolizumab plus cobimetinib; LFT = liver function test; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events and contact the Medical Monitor.

Atezo + Cobi = atezolizumab plus cobimetinib; LFT = liver function test; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c] • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month.
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	• Continue atezolizumab and cobimetinib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab and cobimetinib.*

Atezo + Cobi = atezolizumab plus cobimetinib; LFT = liver function test; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose. • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with *corticosteroid equivalent to* 1−2 mg/kg/day *IV methylprednisolone*. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Atezo + Cobi = atezolizumab plus cobimetinib; BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed*.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib. • For life-threatening immune-mediated hyperthyroidism, withhold cobimetinib. If event becomes clinically manageable within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib; TSH = thyroid-stimulating hormone.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines for atezolizumab in Appendix 6 • Continue cobimetinib.
Hyperglycemia, any grade	• Continue cobimetinib. Consider cobimetinib dose modification per general guidelines as clinically indicated.
Pancreatic events	
Amylase and/or lipase elevation, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib. • For recurrent events, permanently discontinue cobimetinib.
Pancreatitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib.
Pancreatitis, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cobimetinib. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose. If not, permanently discontinue cobimetinib. • For recurrent events, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Pancreatic events (cont.)	
Pancreatitis, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Consider permanently discontinuing cobimetinib. • If cobimetinib is withheld and event resolves to Grade 1 or better within 28 days, resume cobimetinib at current dose. If event does not resolve to Grade 1 or better within 28 days, permanently discontinue cobimetinib.
Neurologic disorder	
Neuropathy, Grade 1, 2, or 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib.
Neuropathy, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cobimetinib. • If patient stabilizes within 28 days, consider resuming cobimetinib at current dose. If not, permanently discontinue cobimetinib.
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cobimetinib. • If patient stabilizes within 28 days, resume cobimetinib at current dose. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Immune-mediated meningoencephalitis, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cobimetinib. • If patient stabilizes within 28 days, resume cobimetinib at current dose. If not, permanently discontinue cobimetinib.
Ocular toxicity	
General guidance	• An ophthalmologist should evaluate visual complaints. Ophthalmology evaluation should include the following: visual acuity testing, intra-ocular pressure measurements, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and optical coherence tomography. A fluorescein angiogram and/or indocyanine green angiogram should be considered, if clinically indicated.
Serous retinopathy, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and cobimetinib. • Continue ophthalmology follow-up as clinically indicated.
Serous retinopathy, Grade 2 (intolerable), Grade 3, or Grade 4	• Withhold cobimetinib. Continue atezolizumab as clinically indicated. • Undergo complete ophthalmologic examination. • If event improves by at least one grade within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Retinal vein occlusion (any grade)	• Permanently discontinue cobimetinib. Continue atezolizumab. • Initiate treatment as per institutional guidelines.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Ocular toxicity (cont.)	
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 1	• Continue atezolizumab and cobimetinib. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 2	• Withhold atezolizumab. Continue cobimetinib. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c]
Potential immune-mediated ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	• Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [c]

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Asymptomatic LVEF decrease from baseline	
LVEF ≥ 50% **or** LVEF 40%–49% with < 10% absolute decrease from baseline	• Continue atezolizumab and cobimetinib.
LVEF < 40% **or** LVEF 40%–49% with ≥ 10% absolute decrease from baseline	• Withhold cobimetinib. Continue atezolizumab as clinically indicated. • Re-evaluate LVEF at 14 days. • If patient has a < 10% absolute decrease from baseline in LVEF, resume cobimetinib with dose reduced by one level. After resuming cobimetinib, re-evaluate LVEF at 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then every 12 weeks (i.e., three cycles) thereafter, or as clinically indicated, until treatment discontinuation. • If patient has an LVEF of < 40% or a ≥ 10% absolute decrease from baseline, permanently discontinue cobimetinib. Continue LVEF assessments every 6 weeks, or as clinically indicated, until LVEF recovers to 50% or to the lower limit of normal.

Atezo + Cobi = atezolizumab plus cobimetinib; LVEF = left ventricular ejection fraction.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Symptomatic LVEF decrease from baseline	• Withhold cobimetinib for at least 4 weeks. Consider withholding atezolizumab. • Patient referral to cardiologist is strongly recommended. • If atezolizumab is withheld, contact the Medical Monitor to discuss resumption of atezolizumab. • Re-evaluate LVEF at 28 days. **Patient is asymptomatic following treatment break:** • If patient has a < 10% absolute decrease from baseline in LVEF, resume cobimetinib with dose reduced by one level. After resuming cobimetinib, re-evaluate LVEF at 2 weeks, 4 weeks, 10 weeks, and 16 weeks and then every 12 weeks (i.e., three cycles) thereafter, or as clinically indicated, until treatment discontinuation. • If patient has an LVEF of < 40% or a ≥ 10% absolute decrease from baseline, permanently discontinue cobimetinib. Continue LVEF assessments every 6 weeks, or as clinically indicated, until LVEF recovers to 50% or to the lower limit of normal. **Patient is symptomatic following treatment break:** • Permanently discontinue cobimetinib. Continue LVEF assessments every 6 weeks, or as clinically indicated, until LVEF recovers to 50% or to the lower limit of normal, or until symptoms resolve.

Atezo + Cobi = atezolizumab plus cobimetinib; LVEF = left ventricular ejection fraction.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Evaluate for cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
Asymptomatic CPK elevation, Grade 1, 2, or 3	• Continue atezolizumab and cobimetinib. • Recheck CPK at least once a week.
Asymptomatic CPK elevation, Grade 4	• Withhold atezolizumab and cobimetinib. • If event resolves to Grade 3 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation (cont.)	
Rhabdomyolysis or symptomatic CPK elevation	• Withhold atezolizumab and cobimetinib. • If event improves by at least one grade and symptoms resolve within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib. • Resumption of atezolizumab may be considered in patients who are deriving benefit.
Hemorrhage	
Grade 3 hemorrhage other than cerebral hemorrhage	• Withhold cobimetinib. Continue atezolizumab. • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Permanently discontinue cobimetinib if event is attributed to cobimetinib; otherwise, withhold cobimetinib. Continue atezolizumab. • Clinical judgment should be applied when considering whether cobimetinib should be resumed (if withheld). There are no data on the effectiveness of cobimetinib dose modifications for hemorrhage events.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Cobi Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicity not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue cobimetinib.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold cobimetinib. • If event resolves to Grade 2 or better within 28 days, resume cobimetinib at current dose. If not, permanently discontinue cobimetinib.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above or in Appendix 6	• Withhold atezolizumab and cobimetinib. • If event resolves to Grade 1 or better within 12 weeks after event onset, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume cobimetinib with dose reduced by one level. If not, permanently discontinue cobimetinib.

Atezo + Cobi = atezolizumab plus cobimetinib.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A8–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + COBI ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Cobi arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular events
  - Retinal vein occlusion
  - Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
  - Ocular inflammatory toxicities (e.g., uveitis, retinitis)
- Significant muscular toxicities
  - Rhabdomyolysis or Grade ≥ 3 creatine phosphokinase elevation

  - Myopathies, including myositis
- Grade ≥ 2 cardiac events, including (but not limited to) the following:
  - Symptomatic heart failure or Grade ≥ 3 LVEF reduction
  - Atrial fibrillation, myocarditis, pericarditis
- Vasculitis
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥ 3 rash
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A8–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + COBI ARM

A8–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A8–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 1 month after the last dose of cobimetinib. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to

cobimetinib. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A8–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A8–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A8–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + COBI ARM

Table 5 Schedule of Activities for Atezo + Cobi Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Days −28 to −1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs [e]		x	x	x	x	x	
Weight [f]		x		x		x	
Complete physical examination [g]						x	
Limited physical examination [f, h]		x		x			
ECOG Performance Status [f]		x		x		x	
ECG [f, i]		Perform as clinically indicated					
ECHO or MUGA scan				x [j]		x [j]	
Ophthalmologic examination [k]				x		x	
Hematology [l]		x [m]	x	x	x	x	
Chemistry [n]		x [m]	x	x	x	x	
TSH, free T3 (or total T3), free T4 [o]		x [m]				x	
Pregnancy test [p]		x		x		x	
Urinalysis [q]		Perform as clinically indicated					
Serum autoantibody sample [r]		Perform if a patient experiences a suspected immune-mediated adverse event					

Table 5 Schedule of Activities for Atezo + Cobi Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Days −28 to −1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
PK samples	See Appendix 2	Refer to Table 6					
ADA samples		Refer to Table 6					
Biomarker samples		Refer to Table 6					
Blood sample for RBR (optional) [s]		x					
Tumor biopsy		x [t]					
Tumor biopsy (optional)		x [u]					
Tumor response assessments		x [v, w, x]					
Concomitant medications [y]		x		x		x	
Adverse events [z]		x	x	x	x	x [z]	x [z]
Atezolizumab administration [aa, bb]		x	x	x	x		
Dispense cobimetinib [bb, cc]		x		x			
Study drug accountability				x [dd]			
Survival follow-up and anti-cancer treatment							x [ee]

ADA = anti-drug antibody; Atezo + Cobi = atezolizumab plus cobimetinib; CT = computed tomography; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; MUGA = multiple-gated acquisition; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.
Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Table 5 Schedule of Activities for Atezo + Cobi Arm (cont.)

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity related to cobimetinib will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Evaluation of left ventricular function, either by ECHO or MUGA scan, will be performed at screening, on Day 1 of Cycle 2 (±1 week), on Day 1 of Cycles 5, 8, 11 (±2 weeks for each), on Day 1 of Cycles 15, 19, 23 (±2 weeks for each), on Day 1 of Cycles 29, 35, 41, 47, and every six cycles thereafter (i.e., Cycles 53, 59, 65, etc.) (±2 weeks for each), at the treatment discontinuation visit (unless evaluation performed within the previous 12 weeks showed no clinically significant findings or changes from baseline), and as clinically indicated.

Table 5 Schedule of Activities for Atezo + Cobi Arm (cont.)

[k] Ophthalmologic examinations (as described in Section 4.5.6) should be performed at screening, on Day 1 of Cycle 2 (±1 week), on Day 1 of Cycles 5, 8, 11 (±2 weeks), on Day 1 of Cycles 15, 19, 23 (±2 weeks), on Day 1 of Cycles 29, 35, 41, 47, and every six cycles thereafter (i.e., Cycles 53, 59, 65, etc.) (±2 weeks for each), at the treatment discontinuation visit (unless examination performed within the previous 12 weeks showed no clinically significant findings or changes since the prior examination), and as clinically indicated.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[n] Chemistry panel (serum or plasma) includes CPK, sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. CPK will be performed only on Day 1 of each cycle. Amylase and lipase will be included at Day 1 of each treatment cycle.

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[p] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[t] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (Stage 1 only) (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[u] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Table 5 Schedule of Activities for Atezo + Cobi Arm (cont.)

[v] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[w] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[x] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

Table 5 Schedule of Activities for Atezo + Cobi Arm (cont.)

[bb] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[cc] Patients will receive cobimetinib at a dose of 60 mg (three 20-mg tablets) orally once a day on Days 1–21 of each cycle. At least 7 days off cobimetinib are required prior to starting a new treatment cycle. Cobimetinib should be taken approximately the same time each day, and no later than 12 hours after the scheduled time. On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel.

[dd] Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance.

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Cobi Arm: Preliminary and Expansion Phases

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to study treatment	• Cobimetinib PK (plasma) • Biomarkers (plasma, serum)
	2–4 hours after cobimetinib dose	• Cobimetinib PK (plasma)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Cobi = atezolizumab plus cobimetinib; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Not performed for patients who enter Stage 2.

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Cobi Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (± 30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) [a] • Atezolizumab ADA (serum) [a]

ADA = anti-drug antibody; Atezo + Cobi = atezolizumab plus cobimetinib; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Not performed for patients who enter Stage 2.

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Appendix 9
Study Details Specific to Atezo + Evo Arm (Stage 1)

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A9–1 BACKGROUND ON ATEZO + EVO ARM

A9–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A9–1.2 BACKGROUND ON EVOLOCUMAB

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was first described in 2003 to play a role in liver regeneration and neuronal differentiation and was later implicated in cholesterol homeostasis (Seidah et al. 2003). In humans, the clinical importance of PCSK9 was highlighted when its gain-of-function mutation was associated with autosomal dominant hypercholesterolemia (Abifadel et al. 2003).

These and multiple subsequent studies led to the development of various strategies to reduce circulating PCSK9 levels—including PCSK9 inhibitors and monoclonal antibodies to PCSK9 like evolocumab and alirocumab—demonstrating a large beneft in the field of atherosclerosis and cardiovascular diseases (Liberale et al. 2017, 2018).

PCSK9 is primarily synthesized in the liver and secreted into the blood. It acts as a major regulator of circulating LDL cholesterol (LDL-C) by binding to hepatic cell surface LDL receptors (LDLRs).

Large Phase III trials demonstrated that both monoclonal antibodies evolocumab and alirocumab produce mean reductions in LDL-C of approximately 60% with a good safety profile, both when used alone or when added to standard statin treatment (Robinson et al. 2015; Giugliano et al. 2017).

Evolocumab is a 154-kDa human monoclonal antibody with high binding affinity for PCSK9 and is approved for the treatment of hypercholesterolemia. Evolocumab has been tested in an extensive study program, consisting of five Phase II studies and seven Phase III studies as well as two open-label extension studies and one outcomes study. Evolocumab has been generally very well tolerated and adverse events have mostly been manageable and reversible. An overview on the safety and efficacy data from clinical studies can be found in Section A9–2.4).

Based on these clinical studies, evolocumab was approved in the European Union in July 2015 for adults with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH] or nonfamilial hypercholesterolemia) as well as for adults and adolescents ≥ 12 years of age with homozygous familial hypercholesterolemia (HoFH).

In the United States, evolocumab was approved in August 2015 for adult patients with HeFH, clinical atherosclerotic cardiovascular disease, or HoFH (who require supplementary LDL-C–lowering treatment in addition to background LDL-lowering therapies [e.g., statins, ezetimibe, LDL apheresis]).

A9–2 RATIONALE FOR ATEZO + EVO ARM

A9–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer.

PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A9–2.2 PCSK9 SIGNALING IN CANCER

Proprotein convertases (PCs) of the subtilisin and kexin family constitute a group of nine calcium-dependent serine proteases: PC1/3, Furin, PC2, PC4, PC5/6, PC7, PACE4 (Thomas 2002), SKI-1 (Seidah et al. 1999), and PCSK9 (Seidah et al. 2003). PCs were associated with cancer since the early 1990s (Smeekens and Steiner 1990), and their expression was found to be different between normal tissue and tumor cells.

Research by Momtazi-Borojeni et al. (2019) demonstrated that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) by vaccination with a nanoliposomal anti-PCSK9 vaccine improved breast cancer outcomes while having no harmful effects in tumor-bearing BALB/C mice inoculated with 4T1 breast carcinoma cells. Furthermore, Abdelwahed et al. (2020) demonstrated that inhibition of PCSK9 by pseurotin A suppressed the progression of hormone-dependent BT-474 breast cancer cells in an orthotopic nude mouse xenograft model by reducing PCSK9 expression on the cancer cells as well as the locoregional recurrence after primary tumor surgical excision.

Importantly, Liu and colleagues (2020) recently discovered that PCSK9 is also a protein of interest in modulating response to immunotherapy. Syngeneic inoculation of mice

with PCSK9-knockout mouse melanoma, mammary cancer, and colon cancer cell lines resulted in substantially reduced tumor growth compared with tumors in mice inoculated with PCSK9–wild-type variants of the same cancer cell lines. Interestingly, this effect was independent of host LDL receptor (LDLR) and cholesterol levels.

Knocking out PCSK9, as well as treatment with either of the two approved PCSK9 antibodies (evolocumab and alirocumab), synergized with anti–PD-1 treatment in all four syngeneic mouse models tested. Strikingly, the anti–PD-1 antibody plus evolocumab combination was efficacious even in anti-PD-1–resistant MC38R colon cancer models. Notably, treatment with evolocumab was effective in this setting either alone or in combination with anti–PD-1 treatment.

Flow cytometric analyses revealed that tumors grown from syngeneically transplanted PCSK9-knockout melanoma cells had substantially increased intratumoral infiltration of $CD8^+$ cytotoxic T cells, $CD4^+$ helper T cells, $\gamma\delta$ T cells, and natural killer cells.

Additionally, the ratio of $CD8^+$ cytotoxic T cells to regulatory T cells was increased in PCSK9-knockout tumors, and interferon (IFN)-γ^+ $CD8^+$ and $GzmB^+$ $CD8^+$ cytotoxic T cells were more abundant in PCSK9-knockout tumors. Depletion of $CD8^+$ cytotoxic T cells eliminated the tumor growth suppression observed in PCSK9 knockout tumors, demonstrating the importance of tumor-infiltrating $CD8^+$ cytotoxic T cells for suppressing tumor growth.

Mechanistically, PCSK9 activity reduced major histocompatibility complex class I (MHC-I) presentation on tumor cell surfaces by physically interacting with this complex and promoting its lysosomal degradation, hence leading to reduced tumor growth upon knockout or inhibition of PCSK9. In summary, the work of Liu et al. (2020) reveals a previously unknown role for PCSK9 independent of its canonical function in the regulation of cholesterol levels and demonstrates the efficacy of combining CPI-treatment with PCSK9 inhibition in CPI-resistant tumor models.

In addition to the data generated by Liu et al. (2020), Yuan et al. (2020) generated supporting evidence for the role of PCSK9 in anti-tumor immune responses by modifying LDLR expression, cholesterol metabolism, and T-cell receptor (TCR) activity in tumor infiltrating lymphocytes. The group demonstrated that intratumoral $CD8^+$ T cells have reduced cholesterol levels, resulting from decreased levels of LDLR on the cell surface. As LDL-derived cholesterol is one of the key resources necessary for $CD8^+$ T cell proliferation and effector function (Kidani et al. 2013; Yang et al. 2016; Proto et al. 2018) and LDL uptake in activated $CD8^+$ T cells is almost completely dependent on LDLR, downregulation of LDLR on the surface of intratumoral $CD8^+$ T cells—by PCSK9-driven internalization of LDLR—can significantly attenuate their proliferative activity.

In addition, the group demonstrated that reduced LDLR expression also affects TCR signaling and the effector functions of $CD8^+$ T cells. LDLR interacts with CD3, a subunit of the TCR complex, modulating the TCR signaling pathway. The phosphorylation of CD3ζ was inhibited in $ldlr^{-/-}$ $CD8^+$ T cells as compared with wild-type $CD8^+$ T cells upon stimulation with anti-CD3 and anti-CD28, thus hampering TCR signal transduction. This demonstrates that CD3ζ phosphorylation and subsequent TCR-signal transduction is inhibited by LDLR deficiency. Furthermore, LDLR deficiency appears to inhibit TCR recycling to the plasma membrane.

Together, these experiments indicate that LDLR interacts with the TCR complex and regulates TCR signaling and expression on the cell surface as an immune regulatory membrane protein.

The investigators also demonstrated that PCSK9 was highly expressed in tumors as compared with normal tissue, and PCSK9 levels were negatively correlated with $CD3^+$ T-cell infiltration, demonstrating that the tumor derived PCSK9 predominantly inhibits $CD8^+$ T cell immune response leading to immune evasion by the tumor. Furthermore, the group also demonstrated that PCSK9 intrinsically inhibits the antitumor activity of $CD8^+$ T cells by decreasing LDLR expression and ultimately down-regulating plasma membrane TCR levels, CD3 phosphorylation, and the effector function.

Inhibiting PCSK9 in the respective syngeneic mouse models effectively inhibited tumor progression, and combination therapy of PCSK9 inhibition and checkpoint inhibition in immunocompetent MC38 tumor burdened C57BL/6 mice resulted in stronger tumor suppressive effect than either monotherapy.

A9–2.3 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH EVOLOCUMAB

Liu et al. (2020) were able to demonstrate that PCSK9 knockout synergized with anti–PD-1 treatment in all four syngeneic mouse models tested, as did treatment with either of the two PCSK9 antibodies (evolocumab or alirocumab) that are currently approved for the treatment of refractory hyperlipidemia (please refer to Sections A9–2.2 and A9–2.4).

In addition to the enhanced efficacy of both treatments in combination—with long-term survival of some host mice—the group was able to demonstrate efficacy of the anti–PD-1 antibody and evolocumab combination in anti-PD-1–resistant MC38R colon cancer models. Notably, treatment with evolocumab and alirocumab was effective either alone or in combination with anti–PD-1 treatment.

The synergistic effect of combining checkpoint blockade and inhibition of PCSK9 in attenuating tumour growth was confirmed by Yuan et al. (2020) in the respective syngeneic mouse models tested.

To validate the role of PCSK9 in cancer in CPI-treated patients with NSCLC, the association between PCSK9 gene expression status and the efficacy of atezolizumab in NSCLC in two clinical trials was retrospectively explored: the Phase III second-line NSCLC trial OAK and the Phase III first-line NSCLC trial IMpower 150.

OAK evaluated the efficacy and safety of atezolizumab as a single agent versus docetaxel in patients with locally advanced or metastatic NSCLC that had progressed during or following treatment with a platinum-containing regimen. The study met its co-primary endpoints of overall survival (OS) in all randomized patients (intent-to-treat [ITT] population) and OS in a PD-L1-selected subgroup in the primary analysis population (tumor cell 1/2/3 or immune cell 1/2/3). Retrospective subgroup analysis of the OAK ITT dichotomized by PCSK9 expression as determined by RNA-sequencing (above or below the median), revealed that atezolizumab demonstrated a significant OS benefit versus docetaxel in PCSK9-low expressors, whereas there was no difference in OS between atezolizumab and docetaxel in the PCSK9-high expressor group.

This finding was consistent with the results of the same analysis of IMpower150 where patients with NSCLC who had high PCSK9 tumor expression derived limited benefit from atezolizumab plus carboplatin plus paclitaxel (ACP) or atezolizumab plus bevacizumab plus carboplatin/paclitaxel (ABCP), although bevacizumab may provide some benefit to PCSK9-high patients. Patients with low PCSK9 expression derived significant benefit from both ACP and ABCP but not from the chemotherapy control. Together these results suggest PCSK9 expression may be predictive of clinical efficacy of atezolizumab.

It was also observed that PCSK9 expression is generally anti-correlated with both immune infiltration and PD-L1 expression in OAK, which may partially explain why PCSK9-high patients show limited benefit from atezolizumab.

Taken together, the existing preclinical and clinical data on the role of PCSK9 in anti-tumor immune response suggest that the PCSK9/LDLR axis is a promising target and combined inhibition of PCSK9 and PD-1/PD-L1 could significantly enhance immunotherapy efficacy and re-sensitize patients to CPI treatment.

A9–2.4 CLINICAL STUDIES WITH EVOLOCUMAB

In randomized placebo-controlled clinical studies, evolocumab doses of 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM) for 12 weeks reduced LDL-C by approximately 55%–75%, compared with placebo, at the mean of Weeks 10 and 12

among patients with primary hyperlipidemia and mixed dyslipidemia who received evolocumab either as monotherapy (Koren et al. 2012, 2014) or in combination with a statin (Giugliano et al. 2012; Robinson et al. 2014) and in patients with HeFH who received evolocumab with a statin (Raal et al. 2012, 2015). In randomized active-control studies, these doses of evolocumab for 12–24 weeks reduced LDL-C by approximately 35%–45% compared with ezetimibe in patients with primary hyperlipidemia and mixed dyslipidemia (Koren et al. 2012, 2014), including patients with documented statin intolerance (Sullivan et al. 2012; Stroes et al. 2014; Nissen et al. 2016).

A9–2.4.1 Adverse Reactions in Adults with Primary Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia)

The data described below reflect exposure to evolocumab in eight placebo-controlled trials that included 2651 patients treated with evolocumab, including 557 patients exposed for 6 months and 515 patients exposed for 1 year (median treatment duration of 12 weeks). The mean age of the population was 57 years; 49% of the population were women; 85% White, 6% Black, 8% Asians, and 2% other races.

Safety Profile in a 52-Week Controlled Trial (DESCARTES, NCT01516879):

In this 52-week, double-blind, randomized, placebo-controlled trial, 599 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 56 years (range: 22 to 75 years); 23% were older than 65 years; 52% were women; 80% White, 8% Black, 6% Asian, and 6% identified as Hispanic ethnicity. Adverse reactions reported in at least 3% of evolocumab-treated patients, and more frequently than in placebo-treated patients in DESCARTES, are shown in Table 1 below. Adverse reactions led to discontinuation of treatment in 2.2% of evolocumab-treated patients and 1% of placebo-treated patients. The most common adverse reaction that led to evolocumab treatment discontinuation and occurred at a rate greater than placebo was myalgia (0.3% vs. 0% for evolocumab and placebo, respectively).

Table 1 Adverse Reactions Occurring in Greater Than or Equal to 3% of Evolocumab-Treated Patients and More Frequently Than with Placebo in DESCARTES

	Placebo (N=302) %	REPATHA (N=302) %
Nasopharyngitis	9.6	10.5
Upper respiratory tract infection	6.3	9.3
Influenza	6.3	7.5
Back pain	5.6	6.2
Injection site reactions	5.0	5.7
Cough	3.6	4.5
Urinary tract infection	3.6	4.5
Sinusitis	3.0	4.2
Headache	3.6	4.0
Myalgia	3.0	4.0
Dizziness	2.6	3.7
Musculoskeletal pain	3.0	3.3
Hypertension	2.3	3.2
Diarrhea	2.6	3.0
Gastroenteritis	2.0	3.0

Safety Profile in Seven Pooled 12-Week Controlled Trials

In seven pooled 12-week, double-blind, randomized, placebo-controlled trials, 993 patients received 140 mg of evolocumab subcutaneously Q2W and 1059 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 57 years (range: 18 to 80 years); 29% were older than 65 years; 49% were women; 85% White, 5% Black, 9% Asian, and 5% identified as Hispanic ethnicity. Adverse reactions reported in at least 1% of evolocumab-treated patients, and more frequently than in placebo-treated patients, are shown in Table 2 below.

Table 2 Adverse Reactions Occurring in Greater Than 1% of Evolocumab-Treated Patients and More Frequently Than with Placebo in Pooled 12-Week Trials

	Placebo (N=1224) %	REPATHA [a] (N=2052) %
Nasopharyngitis	3.9	4.0
Back pain	2.2	2.3
Upper respiratory tract infection	2.0	2.1
Arthralgia	1.6	1.8
Nausea	1.2	1.8
Fatigue	1.0	1.6
Muscle spasms	1.2	1.3
Urinary tract infection	1.2	1.3
Cough	0.7	1.2
Influenza	1.1	1.2
Contusion	0.5	1.0

[a] 140 mg every 2 weeks and 420 mg once monthly combined

Safety Profile in Eight Pooled Controlled Trials (Seven 12-Week Trials and One 52-Week Trial)

The adverse reactions described below are from a pool of the 52-week trial (DESCARTES) and seven 12-week trials. The mean and median exposure durations of evolocumab in this pool of eight trials were 20 weeks and 12 weeks, respectively.

- Local Injection Site Reactions: Injection site reactions occurred in 3.2% and 3.0% of evolocumab-treated and placebo-treated patients, respectively. The most common injection-site reactions were erythema, pain, and bruising. The proportions of patients who discontinued treatment due to local injection-site reactions in evolocumab-treated patients and placebo-treated patients were 0.1% and 0%, respectively.
- Allergic reactions: Allergic reactions occurred in 5.1% and 4.7% of evolocumab-treated and placebo-treated patients, respectively. The most common allergic reactions were rash (1.0% vs. 0.5% for evolocumab and placebo, respectively), eczema (0.4% vs. 0.2%), erythema (0.4% vs. 0.2%), and urticaria (0.4% vs. 0.1%).

A9–2.4.2 Safety Profile in Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial (evolocumab Cardiovascular Outcomes Trial, FOURIER, NCT01764633), 27525 patients received at least one dose of evolocumab or placebo [see Clinical Studies (14.1)]. The mean age was 62.5 years (range: 40 to 86 years); 45% were 65 years or older, 9% were 75 years or older; 25% were women; 85% White, 2% Black, 10% Asian, and 8% identified as Hispanic ethnicity. Patients were exposed to evolocumab or placebo for a median of 24.8 months; 91% of patients were exposed for $\geq$12 months, 54% were exposed for $\geq$24 months, and 5% were exposed for $\geq$36 months. The safety profile of evolocumab in this trial was generally consistent with the safety profile described above in the 12- and 52-week controlled trials involving patients with primary hyperlipidemia (including HeFH). Serious adverse events occurred in 24.8% and 24.7% of evolocumab-treated and placebo-treated patients, respectively. Adverse events led to discontinuation of study treatment in 4.4% of patients assigned to evolocumab and 4.2% assigned to placebo. Common adverse reactions ($>$5% of patients treated with evolocumab and occurring more frequently than placebo) included diabetes mellitus (8.8% evolocumab, 8.2% placebo), nasopharyngitis (7.8% evolocumab, 7.4% placebo), and upper respiratory tract infection (5.1% evolocumab, 4.8% placebo).

A9–2.4.3 Safety Profile in Patients with Homozygous Familial Hypercholesterolemia

In a 12-week, double-blind, randomized, placebo-controlled trial of 49 patients with HoFH (TESLA, NCT01588496), 33 patients received 420 mg of evolocumab subcutaneously QM. The mean age was 31 years (range: 13–57 years); 49% were

women; 90% White, 4% Asian, and 6% other. The adverse reactions that occurred in at least two (6.1%) evolocumab-treated patients, and more frequently than in placebo-treated patients, included:

- Upper respiratory tract infection (9.1% vs. 6.3%)
- Influenza (9.1% vs. 0%)
- Gastroenteritis (6.1% vs 0%)
- Nasopharyngitis (6.1% vs. 0%)

A9–2.4.4 Immunogenicity

In clinical studies, 48 out of 17,992 patients (0.3%) treated with at least one dose of evolocumab tested positive for binding antibody development. The patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies, and none of the patients tested positive for neutralizing antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab.

A9–2.4.5 Drug Interactions

As monoclonal antibodies have a low potential for pharmacokinetic drug interactions, no in vitro and in vivo drug interaction studies have been performed for evolocumab so far. However, the pharmacokinetic interaction between statins and evolocumab was evaluated in clinical trials. An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of PCSK9, which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab.

Refer to the Evolocumab Summary of Product Characteristics for details on nonclinical and clinical studies.

A9–2.5 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population. Two important mechanisms of resistance to CPI treatment, particularly in this growing population of CPI-experienced patients, is decreased antigen presentation (e.g., by downregulation of MHC-1 on the cell surface via PCSK9) and impaired TCR function. Taking into account the potentially synergistic mechanisms of action of atezolizumab and PCSK9 inhibition by evolocumab that has been well demonstrated in preclinical studies, as well as the known, manageable, and very tolerable safety profile for each of these agents, combination treatment with these two agents appears to have a very promising therapeutic potential for solid tumors such as NSCLC.

Furthermore, the current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected on the basis of known safety profile of the combination partners. In addition, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion and exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee and a Scientific Oversight Committee.

Given the well-controlled Phase Ib setting and the tolerable safety profile of both drugs, together with the promising preclinical and retrospective clinical data, the benefit–risk ratio for testing the combination of atezolizumab and evolocumab in NSCLC is positive.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A9–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + EVO ARM

A9–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at the approved fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A9–3.2 RATIONALE FOR EVOLOCUMAB DOSE AND SCHEDULE

Evolocumab will be administered subcutaneously at the approved fixed dose of 140 mg Q2W on Days 1 and 15 of each 28-day cycle.

A9–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + EVO ARM

A9–4.1 TREATMENT IN ATEZO + EVO ARM

A9–4.1.1 Formulation, Packaging, and Handling

A9–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A9–4.1.1.2 Evolocumab

Evolocumab will be supplied as 140 mg/mL solution in a single-use pre-filled SureClick® autoinjector

For information on the formulation and handling of evolocumab, see the pharmacy manual and the Evolocumab Summary of Product Characteristics.

A9–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Evo arm will receive treatment as outlined in Table 3 until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 3 Treatment Regimen for Atezo + Evo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Atezolizumab 840 mg IV on Days 1 and 15 • Evolocumab 140 mg SC on Days 1 and 15

Atezo = atezolizumab; Evo = evolocumab

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF) and reported under “special situations” as explained under Section 5.3.5.12. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or evolocumab are available.

A9–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A9–5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). *The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A9–4.1.2.2 Evolocumab Administration

Evolocumab will be administered by SC injection at a fixed dose of 140 mg on Days 1 and 15 of each 28-day cycle.

- Administer evolocumab subcutaneously into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated using a single-use prefilled syringe.
- Do not co-administer evolocumab with other injectable drugs at the same administration site.
- Rotate the site of each SC administration (abdomen, thigh, or upper arm)

If an evolocumab dose is missed, administer evolocumab within 7 days from the missed dose and resume the original schedule. If dose is not administered within 7 days, wait until the next dose on the original schedule.

No dose modification for evolocumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A9–5.1.4. Evolocumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A9–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to atezolizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 5, provided they meet the eligibility criteria for Stage 2 (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 5 Stage 2 Treatment Regimens Available for the Atezo + Evo Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Evo = evolocumab; Lina = linagliptin.

Refer to Appendix 16 and Appendix 17 for details specific to the atezolizumab plus docetaxel arm, and atezolizumab plus linagliptin arm, respectively.

A9–4.2 CONCOMITANT THERAPY FOR ATEZO + EVO ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A9–4.2.1 Permitted Therapy for Atezo + Evo Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A9–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and evolocumab may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the criteria listed below are met.

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anticonvulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A9–4.2.2 and A9–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence on potential interactions of COVID-19 vaccines with evolocumab. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A9–4.2.2 Cautionary Therapy for Atezo + Evo Arm

A9–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A9–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A9–4.2.3) may be used during the study at the discretion of the investigator.

A9–4.2.3 Prohibited Therapy for Atezo + Evo Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A9–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A9–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + EVO ARM

Contraception requirements for women and men in the Atezo + Evo arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab and for 3 months after the final dose of evolocumab

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic

abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A9–5 ASSESSMENT OF SAFETY FOR ATEZO + EVO ARM

A9–5.1 SAFETY PLAN FOR ATEZO + EVO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and evolocumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A9–5.1.1, A9–5.1.2, and A9–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A9–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A9–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A9–5.1.2 Risks Associated with Evolocumab

The most common side effects (in more than 5% of patients in clinical studies) of evolocumab include nasopharyngitis, upper respiratory tract infections, influenza, diabetes mellitus, back pain, injection-site reactions, and allergic reactions.

The most common adverse reactions in clinical trials in primary hyperlipidemia (including HeFH, in more than 5% of patients treated with evolocumab and occurring more frequently than placebo) include nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection-site reactions, and allergic reactions.

The most common adverse reactions in the cardiovascular outcomes trial (in more than 5% of patients treated with evolocumab and occurring more frequently than placebo) include diabetes mellitus, nasopharyngitis, and upper respiratory tract infection.

For more details regarding the safety profile for evolocumab, refer to section A9–2.4 in this appendix as well as the evolocumab prescribing information.

A9–5.1.3 Risks Associated with Combination Use of Atezolizumab and Evolocumab

There are no significant overlapping toxicities associated with combination use of atezolizumab and evolocumab

A9–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Evo Arm

A9–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or evolocumab in this study.

A9–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) . The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Evolocumab treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If evolocumab has been withheld for > 28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved *at the investigator's discretion. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

If atezolizumab is discontinued, evolocumab should also be discontinued. If evolocumab is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A9–4.1.2 for information on dose interruptions for reasons other than toxicity.

A9–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 6. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.*

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Management
Pulmonary events including pneumonitis	
Pulmonary event, Grade 1	• Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab.
Pulmonary event, Grade 2	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Pulmonary event, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6 • Permanently discontinue atezolizumab and evolocumab and contact Medical Monitor. [b]
Endocrine events	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]

[a] If evolocumab has been withheld for >28 days after event onse tbecause of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved *at the investigator's discretion. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Management
Endocrine events (cont.)	
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab **TSH < 0.1 mU/L:** • Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Symptomatic adrenal insufficiency, Grade 2–4	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Hyperglycemia, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab

TSH = thyroid-stimulating hormone.

[a] If evolocumab has been withheld for > 28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved *at the investigator's discretion. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Management
Endocrine events (cont.)	
Hyperglycemia, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Follow guidelines for atezolizumab in Appendix 6 • Withhold evolocumab; evolocumab can be resumed once atezolizumab treatment is resumed [a]
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and evolocumab and contact Medical Monitor [b]
Evolocumab-related toxicities not described above	
Grade 1 or 2	• Continue evolocumab and atezolizumab
Grade 3	• Withhold evolocumab treatment; continue atezolizumab • If event resolves to Grade 2 within 28 days, resume evolocumab. If not, permanently discontinue evolocumab. • If event resolves to Grade 1 or better within 28 days, resume evolocumab. If not, permanently discontinue evolocumab
Grade 4	• Withhold evolocumab and atezolizumab • If event resolves to Grade 1 or better within 28 days, resume evolocumab. If not, permanently discontinue evolocumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.

[a] If evolocumab has been withheld for >28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved *at the investigator's discretion. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Management
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab
Grade 3	• Follow guidelines for atezolizumab in Appendix 6 • Continue evolocumab
Grade 4	• Follow guidelines for atezolizumab in Appendix 6 • If atezolizumab is discontinued, evolocumab should also be discontinued.

[a] If evolocumab has been withheld for > 28 days after event onset because of toxicity, the patient should be discontinued from evolocumab, unless resumption of treatment is approved *at the investigator's discretion. The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A9–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + EVO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Evo arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A9–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + EVO ARM

A9–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of atezolizumab and 3 months after the last dose of evolocumab. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue atezolizumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A9–5.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A9–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A9–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + EVO ARM

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs [e]		x	x	x	x	x	
Weight [f]		x		x		x	
Complete physical examination [g]						x	
Limited physical examination [f, h]		x	x	x	x		
ECOG Performance Status [f]		x		x		x	
ECG [f, i]		Perform as clinically indicated					
Hematology [j]		x [k]	x	x	x	x	
Chemistry [l]		x [k]	x	x	x	x	
Coagulation (INR and aPTT)		x [k]	x	x	x	x	
Fasting lipid panel [m]		x [k]				x	
TSH, free T3 (or total T3), free T4 [n]		x [k]				x	
Pregnancy test [o]		x [k]		x		x	x
Blood sample for blood-based NGS ctDNA test						x	
Urinalysis [p]		Perform as clinically indicated					

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1) (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
Serum autoantibody sample [q]	See Appendix 2	Perform if a patient experiences a suspected immune-mediated adverse event					
PK samples		Refer to Table 8 below					
ADA samples		Refer to Table 8 below					
Biomarker samples		Refer to Table 8 below					
Blood sample for RBR (optional) [r]		x					
Tumor biopsy		x [s]					
Tumor biopsy (optional)		x [t]					
Tumor response assessments		x [u, v, w]					
Concomitant medications [x]		x	x	x	x	x	
Adverse events [y]		x	x	x	x	x [y]	x [y]
Atezolizumab administration [z, aa]		x	x	x	x		
Evolocumab administration [z, bb]		x	x	x	x		
Survival follow-up and anti-cancer treatment							x [cc]

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1) (cont.)

ADA = anti-drug antibody; Atezo = atezolizumab; CT = computed tomography; ctDNA = circulating tumor DNA; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; Evo = evolocumab; NGS = next generation sequencing; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity to evolocumab will be given the option of receiving a different treatment combination in Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1) (cont.)

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] Fasting lipid panel (cholesterol, HDL, LDL, and triglyceride) will be assessed (after ≥ 8 hr of fasting) on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[o] All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[r] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[s] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[t] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1) (cont.)

[u] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[v] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[w] For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

[x] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[y] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[z] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[aa] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with

Table 7 Schedule of Activities for Atezo + Evo Arm (Stage 1) (cont.)

the previous infusion. Refer to Section A9–4.1.1.1 for details on atezolizumab infusions (including measurement of vital signs).

[bb] Evolocumab will be administered by SC injection at a fixed dose of 140 mg on Days 1 and 15 of each 28-day cycle. Refer to Section A9–4.1.2.2 for details on evolocumab injections.

[cc] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 8 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Evo Arm

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Evolocumab PK (serum) • Evolocumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo + Evo = atezolizumab plus evolocumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 10
Study Details Specific to Docetaxel Arm (Control for Cohort 2)

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A10–1 MATERIALS AND METHODS SPECIFIC TO DOCETAXEL ARM

A10–1.1 TREATMENT IN DOCETAXEL ARM

A10–1.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of docetaxel, refer to the local prescribing information.

A10–1.1.2 Dosage, Administration, and Compliance

Patients in the docetaxel arm will receive treatment as outlined in Table 1 until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Treatment must be initiated no later than 7 days after treatment assignment.

Table 1 Treatment Regimen for Docetaxel Arm

Cycle Length	Dose, Route, and Regimen
21 days	• Docetaxel 75 mg/m^2 IV over 60 minutes on Day 1 of each cycle

Docetaxel will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. To reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions, patients should be premedicated with corticosteroids according to local practice (e.g., 8 mg of oral dexamethasone administered twice daily) for 3 days, starting 1 day prior to docetaxel administration. Anti-emetic medications may be administered prophylactically according to local practice at the investigator's discretion.

Guidelines for docetaxel dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A10–2.1.2. Docetaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Any overdose or incorrect administration of docetaxel should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. For information on overdosing of docetaxel, refer to the local prescribing information for each agent.

A10–1.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 or unacceptable toxicity related to docetaxel will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 2, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of disease progression or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 2 Stage 2 Treatment Regimens Available for the Docetaxel Arm

Study Treatment	Appendix
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Lina = linagliptin.

Refer to Appendix 17 for details specific to the atezolizumab plus linagliptin arm.

A10–1.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR DOCETAXEL ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for docetaxel, refer to the local prescribing information.

A10–1.3 CONTRACEPTION REQUIREMENTS FOR DOCETAXEL ARM

Contraception requirements for women and men in the docetaxel arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 6 months after the last dose of docetaxel

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 6 months after the last dose of docetaxel. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of docetaxel to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A10–2 ASSESSMENT OF SAFETY FOR DOCETAXEL ARM

A10–2.1 SAFETY PLAN FOR DOCETAXEL ARM

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of docetaxel will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A10–2.1.1 Risks Associated with Docetaxel

The most common side effects of docetaxel include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

For more details regarding the safety profile for docetaxel, refer to the docetaxel prescribing information.

A10–2.1.2 Management of Patients Who Experience Specific Adverse Events in Docetaxel Arm

A10–2.1.2.1 Dose Modifications

The dose of docetaxel can be reduced to 55 mg/m^2 (e.g., for management of drug-related toxicities). If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

A10–2.1.2.2 Treatment Interruption for Toxicities

Docetaxel treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table 3). If docetaxel has been withheld for >63 days because of toxicity, the patient should be discontinued from docetaxel.

Refer to Section A10–1.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A10–2.1.2.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 3. The investigator may use discretion in adhering to the guidelines described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm

Event	Action to Be Taken
Hematologic toxicity	
Nadir ANC $< 0.5 \times 10^9$/L (500/μL) for ≥ 7 days [a] **or** Febrile neutropenia	First occurrence • Withhold docetaxel. • If event resolves to ANC $\geq 1.5 \times 10^9$/L (1500/μL) within 63 days, [b] and platelet count is $\geq 100 \times 10^9$/L (100,000/μL), resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Hepatotoxicity	
ALT/AST > 1.5 × ULN in combination with ALP > 2.5 × ULN	• Withhold docetaxel. • If event resolves to baseline within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel.
Bilirubin > 1 × ULN **or** ALT/AST > 3.5 × ULN in combination with ALP > 6 × ULN	• Permanently discontinue docetaxel.

ULN = upper limit of normal.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Neurologic toxicity	
Grade 1 or 2	• Continue docetaxel.
Grade 3	First occurrence • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Grade 4	• Permanently discontinue docetaxel.
Hypersensitivity reaction	
Grade 1 or 2	• Continue docetaxel at the discretion of the investigator.
Grade 3 or 4	• Immediate discontinuation of the docetaxel infusion and aggressive therapy. Permanently discontinue docetaxel.
Pleural effusion	
Grade 1	• Continue docetaxel. • Monitor patient closely for possible exacerbation.
Grade 2	• Continue docetaxel. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). • Monitor patient closely (e.g., by ultrasound Q2W). • Consider thoracentesis if clinically indicated. • Consider consultation with thoracic surgeon.
Grade 3	First occurrence • Withhold docetaxel treatment until resolution to Grade $\leq$ 1. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • Consider consultation with thoracic surgeon. • If event resolves to Grade $\leq$ 1 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel. • Consider treatment measures as outlined for first occurrence.

Q2W = every 2 weeks.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Pleural effusion (cont.)	
Grade 4	• Permanently discontinue docetaxel. • Consider treatment measures as outlined for Grade 3 events.
Pericardial effusion	
Grade 2	• Continue docetaxel. • Monitor patient closely for possible exacerbation. • Consider initiation of standard treatment measures. • Consider consultation with cardiologist.
Grade 3	First occurrence • Withhold docetaxel until resolution to Grade ≤ 2. • Monitor patient closely (e.g., by ECG and echocardiography weekly). • Initiate standard treatment measures. • Consider consultation with cardiologist. • If event resolves to Grade ≤ 2 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel. • Consider treatment measures as outlined for first occurrence.
Grade 4	• Permanently discontinue docetaxel. • Consider treatment measures as outlined for Grade 3 events.
Ascites	
Grade 1	• Continue docetaxel. • Monitor patient closely for possible exacerbation.
Grade 2	• Continue docetaxel. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). • Monitor patient closely (e.g., by ultrasound Q2W). • Consider paracentesis if clinically indicated.

Q2W = every 2 weeks.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Ascites (cont.)	
Grade 3	<u>First occurrence</u> • Withhold docetaxel treatment until resolution to Grade ≤ 1. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • Monitor patient closely (e.g., by ultrasound Q2W). • Consider paracentesis if clinically indicated. • If event resolves to Grade ≤ 1 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Consider treatment measures as outlined for first occurrence.
Grade 4	• Permanently discontinue docetaxel. • Consider treatment measures as outlined for Grade 3 events.
Fluid retention (other than pleural effusion, pericardial effusion, or ascites)	
Grade 1	• Continue docetaxel.
Grade 2	• Continue docetaxel. • Monitor patient closely. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic).
Grade 3	<u>First occurrence</u> • Withhold docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic).

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Docetaxel Arm (cont.)

Event	Action to Be Taken
Non-hematologic toxicity not described above	
Grade 1 or 2	• Continue docetaxel.
Grade 3	First occurrence • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Grade 4	• Permanently discontinue docetaxel.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for >63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose will not be escalated during subsequent administrations.

A10–2.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR DOCETAXEL ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the docetaxel arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

A10–2.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN DOCETAXEL ARM

A10–2.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of docetaxel. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue docetaxel and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A10–2.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of docetaxel. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A10–2.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A10–2.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A10–3 SCHEDULE OF ACTIVITIES FOR DOCETAXEL ARM

Table 4 Schedule of Activities for Docetaxel Arm

Assessment/Procedure	Screening	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥2		
	Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available				
Vital signs [e]		x	x	x	x	
Weight [f]		x		x	x	
Complete physical examination [g]					x	
Limited physical examination [f, h]		x	x	x		
ECOG Performance Status [f]		x		x	x	
ECG [f, i]		Perform as clinically indicated				
Hematology [j]		x [k]	x	x	x	
Chemistry [l]		x [k]	x	x	x	
Pregnancy test [m]		x		x	x	
Blood sample for blood-based NGS ctDNA test					x	
Urinalysis [n]		Perform as clinically indicated				
Serum autoantibody sample [o]						
Plasma and serum samples for biomarkers		x [p]	x [p]	x [p]	x [p]	
PBMC sample for biomarkers		x [q]		x [q]		

Table 4 Schedule of Activities for Docetaxel Arm (cont.)

Assessment/Procedure	Screening	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥2		
	Days –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months (±7 days)
Blood sample for RBR (optional) [r]	See Appendix 2	x				
Tumor biopsy		x [s]				
Tumor biopsy (optional)		x [t]				
Tumor response assessments		x [u, v, w]				
Concomitant medications [x]		x	x	x	x	
Adverse events [y]		x	x	x	x [y]	x
Docetaxel administration [z]		x		x		
Survival follow-up and anti-cancer treatment						x [aa]

CT = computed tomography; ctDNA = circulating tumor DNA; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; MUGA = multiple-gated acquisition; NGS = next-generation sequencing; PBMC = peripheral blood mononuclear cell; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience disease progression per RECIST v1.1, as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

Table 4 Schedule of Activities for Docetaxel Arm (cont.)

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[n] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Table 4 Schedule of Activities for Docetaxel Arm (cont.)

[o] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[p] Plasma and serum samples for biomarker analyses will be collected on Days 1 and 15 of Cycle 1, Day 1 of Cycles 2, 4, and 8, and at treatment discontinuation.

[q] PBMC samples for biomarker analyses will be collected on Day 1 of Cycles 1 and 2.

[r] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[s] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or disease progression per RECIST v1.1 (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[t] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[u] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[v] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[w] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of radiographic disease progression according to RECIST v1.1 during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[x] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

Table 4 Schedule of Activities for Docetaxel Arm (cont.)

[y] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[z] Docetaxel will be administered by IV infusion at a dose of 75 mg/m^2 IV over 60 minutes on Day 1 of each cycle. Treatment will continue until unacceptable toxicity or radiographic disease progression according to RECIST v1.1.

[aa] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 11
Study Details Specific to Atezo + Ipat Arm

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A11–1 BACKGROUND ON ATEZO + IPAT ARM

A11–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A11–1.2 BACKGROUND ON IPATASERTIB

Ipatasertib (GDC-0068) is a novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt and is potent in nonclinical models, including tumors with loss of PTEN (PTEN-low, PTEN-null, or PTEN-mutated) or mutations of PIK3CA both in vitro and in vivo. Ipatasertib inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein, resulting in G1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012).

Ipatasertib shows anti-tumor activity in nonclinical models of multiple tumors, including robust single-agent activity in xenograft models with PI3K/Akt pathway activation (e.g., via PTEN loss and/or PIK3CA mutation), including breast, prostate, gastric and ovarian cancer models (Genentech data on file; Ipatasertib Investigator’s Brochure), as well as in patients with cancer.

Ipatasertib is currently being tested as a single agent and in combination with chemotherapy, CIT agents, hormonal agents, or targeted agents in Phase I, Phase II, and Phase III clinical trials.

Ipatasertib has been generally well tolerated, and adverse events have been manageable and reversible.

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies.

A11–2 RATIONALE FOR ATEZO + IPAT ARM

A11–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable

clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A11–2.2 PI3K/AKT SIGNALING IN NSCLC

Akt is the central node of the PI3K-Akt-mammalian target of rapamycin (mTOR) signaling axis and represents a major downstream effector of receptor tyrosine kinases. Activation of the PI3K/Akt pathway results in essential cellular functions including cell survival, growth, and proliferation, which are properties that underlie human cancers. The PI3K/Akt pathway can be activated through loss of the tumor suppressor PTEN (Li et al. 1997), through activating mutations and/or amplifications in PIK3CA (Bachman et al. 2004), or activating mutations in AKT1 (Carpten et al. 2007).

Activation of the PI3K/Akt/mTOR pathway occurs in up to 60% of squamous cell NSCLCs and in around 35% of adenocarcinomas of the lung (Sun et al. 2015). In squamous cell NSCLC, these activations are mostly caused by PIK3CA amplifications in the 3q locus (33%–37%); in adenocarcinoma, the prevalence of PIK3CA amplification is significantly lower (5%–6.2%) and the activations are typically caused by different gene mutations (Yamamoto et al. 2008; Spoerke et al. 2012). The high prevalence of PIK3CA amplifications in squamous cell NSCLC may indicate that these play a pivotal role in the pathogenesis of this tumor.

Another mechanism causing activation of the PI3K/Akt/mTOR pathway are mutations or loss of heterozygosity of PTEN. Although rare (<6%), these are considered to be potential driver mutations in NSCLC (Forgacs et al. 1998; Yokomizo et al. 1998; Marsit et al. 2005; Yanagawa et al. 2012; Kim et al. 2013). In contrast to PTEN mutations, loss of PTEN protein expression (as defined by an absence of staining of tumor cell cytoplasm) occurs more frequently in NSCLC (41.4%–74%) and is reported to be a poor prognostic factor (Marsit et al. 2005; Yanagawa et al. 2012; Tang et al. 2006). PTEN loss is also reported to occur more frequently in squamous cell NSCLC than in adenocarcinoma of the lung (59% and 34%, respectively) (Yanagawa et al. 2012).

Mutations in the AKT1 gene, namely in the pleckstrin homology domain, are associated with increased membrane localization, which results in increased autophosphorylation of AKT1. Although frequent in other tumors such as breast, ovarian, and colorectal tumors (Carpten et al. 2007), these mutations occur less frequently in NSCLC (0–1.9%). Interestingly, all reported NSCLC tumors harboring the AKT1 mutation had squamous cell histology (Do et al. 2010).

Mutations in the KRAS gene, on the contrary, are considered to be a dominant determinant of resistance to EGFR-TKIs and PI3K/Akt/mTOR inhibitors (Shigematsu et al. 2005; Tam et al. 2006; Ihle et al. 2009). This molecular alteration

occurs in 16%–30% of NSCLC. It has been shown that the frequency of KRAS mutations is higher in adenocarcinoma of the lung (10%–30.6%) than in squamous cell NSCLC (5%–9%) (Shigematsu et al. 2005; Tam et al. 2006; Zhu et al. 2008; Gao et al. 2010; Paik et al. 2011; Acquaviva et al. 2012).

Given the fact that the immunologic effects of ipatasertib seem to be independent of PI3K pathway alterations (please refer to Section A11–2.3), this study arm will enroll squamous and non-squamous NSCLC patients despite the potential differences in the prevalence of PI3K-pathway alterations.

A11–2.3 BENEFIT–RISK ASSESSMENT

Recently, nonclinical and clinical data have indicated a correlation between PTEN loss and impaired anti-tumor immune responses, including reduced CD8 T-cell infiltration and reduced efficacy of anti-PD1 therapy in melanoma patients (Peng et al. 2016). Furthermore, nonclinical studies reveal synergistic anti-tumor responses when combining PI3K-Akt pathway inhibition and PD-L1/PD-1 axis blockade. In addition, Akt inhibitors may restore and enhance the physiological function of T cells in the tumor microenvironment and enhance expansion of tumor-specific lymphocytes with memory cell phenotype (Crompton et al. 2015). Concurrent treatment with ipatasertib may enhance checkpoint inhibitor efficacy by driving development of memory T cells over effector T cells, thereby enabling a long-term response in patients (Gubser et al. 2013; Xue et al. 2015). Very recently, Lopez (2020) demonstrated that ipatasertib effectively depleted the tumor microenvironment from CD4+ FOXP3+ regulatory T cells. This effect on the tumor microenvironment was regardless of tumor PI3K/Akt pathway mutation status. In addition, the combination of atezolizumab and ipatasertib resulted in a significant increase in infiltrating effector T cells in the tumor microenvironment after 1 cycle of treatment, with promising preliminary clinical activity.

In an ongoing Phase Ib study of the combination of ipatasertib, atezolizumab, and taxane chemotherapy in first-line, locally advanced/unresectable or metastatic triple-negative breast cancer (TNBC) (Study CO40151), data from the first 26 patients enrolled indicated that treatment was generally tolerable with no new safety signals, no Grade 4 or Grade 5 events, and encouraging preliminary clinical activity (data cutoff date of 5 January 2019; Roche internal data). In addition, the combination of ipatasertib and atezolizumab is also being investigated in ongoing Phase Ib studies in metastatic hormone receptor–positive, HER2-negative breast cancer (Study CO39611) and metastatic TNBC (Study CO40115). As of the data cutoff dates of 30 November and 15 November 2018, respectively, a total of 6 patients each had been treated with atezolizumab and ipatasertib in the two studies. Based on the safety analyses of the first 6 patients dosed in each study, no new safety signals were identified.

The current study (BO39610) contains all safety measures of an early development study in that it enrolls only a well-defined patient population with good performance status selected based on the known safety profile of the combination partners. At the same time, the study implements close safety monitoring, including frequent visits of patients to the site, strict inclusion/exclusion criteria, regular investigator calls, and the implementation of an Internal Monitoring Committee (IMC) and a scientific oversight committee (SOC).

On the basis of these results as well as the tolerable safety profiles of atezolizumab and ipatasertib, combination treatment with these two agents can be safely investigated and is expected to have promising therapeutic potential in solid tumors such as NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A11–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + IPAT ARM

A11–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A11–3.2 RATIONALE FOR IPATASERTIB DOSE AND SCHEDULE

Ipatasertib will be administered orally at a fixed dose of 400 mg once a day (QD) on Days 1–21 of each 28-day cycle. This dose and schedule were selected on the basis of safety data from Arm C of Study PAM4983g, the Phase Ib trial of ipatasertib combined with paclitaxel. In this study, ipatasertib was generally well tolerated when administered at a dose of 400 mg QD on a 21/7 dosing schedule (21 days on and 7 days off), in combination with paclitaxel 90 mg/m^2 administered weekly (3 weeks on and 1 week off). A relative bioavailability and food-effect study (GO29868) was conducted in healthy volunteers. The study confirmed that the Phase III tablet formulation of ipatasertib to be used in this study is anticipated to provide exposures similar to the exposures of

ipatasertib powder-in-capsule and Phase II tablet formulations used in the Phase I (PAM4743g, PAM4983g) and Phase II (GO29227) studies, respectively.

A11–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + IPAT ARM

A11–4.1 TREATMENT IN ATEZO + IPAT ARM

A11–4.1.1 Formulation, Packaging, and Handling

A11–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A11–4.1.1.2 Ipatasertib

Ipatasertib will be supplied as 100-mg tablets packaged in high-density polyethylene bottles for oral administration. For information on the formulation and handling of ipatasertib, see the Ipatasertib Investigator's Brochure.

A11–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Ipat arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + Ipat Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Ipatasertib 400 mg by mouth once daily on Days 1–21 • Atezolizumab 840 mg IV on Days 1 and 15

Atezo + Ipat = atezolizumab plus ipatasertib.

Refer to Section A11–5.1.4.2 for information on treatment interruptions for patients who experience toxicities. Atezolizumab or ipatasertib treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of*

treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab and ipatasertib are available to date.

A11–4.1.2.1 Ipatasertib

Patients will receive ipatasertib at a dose of 400 mg (four 100-mg tablets) orally once a day on Days 1–21 of each 28-day cycle. Ipatasertib should be taken approximately the same time each day and no earlier or later than 4 hours from the scheduled time. Ipatasertib may be taken with or without a meal. Ipatasertib should be swallowed whole with a minimum of 3 ounces (90 mL) of water and should not be chewed, cut, or crushed. On Day 15 of Cycle 1, patients should take their tablets at the clinic prior to the atezolizumab infusion, as directed by site personnel. If a dose of ipatasertib is missed (i.e., not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. If any treatment component is interrupted (dose hold), the study cycle day count continues and does not shift. At the discretion of the investigator, if ipatasertib treatment is withheld because of toxicity, the patient is encouraged to make up the missed doses during the 7 days-off week for ipatasertib, so that 21 daily doses in every 28 days is maintained.

Loperamide (2 mg oral twice a day, or per local institutional guidelines) will be administered daily as prophylaxis for diarrhea in the first cycle. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgment.

In order to assess the actual intake of ipatasertib and of anti-diarrheal medication use, patients should complete a medication diary each day. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed anti-diarrheal medications, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib dosing and specifically any anti-diarrheal used (prescribed or over-the-counter) taken on that cycle of treatment. The intake of loperamide (or other medication for diarrhea prophylaxis) will be reported in the Concomitant Medications eCRF.

Antihistamine is strongly recommended for rash prophylaxis at the first cycle and at the discretion of the investigator for second and subsequent cycles.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A11–5.1.4.2.

A11–4.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation are provided in Section A11–5.1.4.2.

A11–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to ipatasertib will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 3, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible.

Tumor assessments performed prior to or at the time of disease progression or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + Ipat Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Ipat = ipatasertib; Lina = linagliptin.

A11–4.2 CONCOMITANT THERAPY FOR ATEZO + IPAT ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A11–4.2.1 Permitted Therapy for Atezo + Ipat Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A11–4.2.3).

- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab may be continued during palliative radiotherapy.

  Treatment with ipatasertib should be temporarily held for at least 14 days after radiation. The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered. For single-day radiotherapy, this hold may be shorter, *at the investigator's discretion. The Medical Monitor is available to advise as needed.*

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience

infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence to suggest an interaction between ipatasertib and COVID-19 vaccines. The investigator should use clinical judgement to determine the recommendation for and most appropriate timing of the vaccination. COVID-19 vaccines should be administered in accordance with the approved vaccine label and documented in the CRF as concomitant medication.

A11–4.2.2 Cautionary Therapy for Atezo + Ipat Arm

A11–4.2.2.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *T*he Medical Monitor *is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A11–4.2.2.2 Surgery or Radiation

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and ipatasertib should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). After the temporary treatment hold is complete, ipatasertib may be re-initiated when the patient has sufficiently recovered. For minor surgeries or single-day radiotherapy, this hold may be shorter *at the investigator's discretion. The Medical Monitor is available to advise as needed.*

A11–4.2.2.3 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be

avoided during ipatasertib treatment because ipatasertib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).

Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during ipatasertib treatment because they increase the metabolism of ipatasertib. Selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

CYP3A4/5 substrates with a narrow therapeutic index, such as, but not limited to, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine should also be avoided during ipatasertib treatment.

Patients who require short-term use of a strong CYP3A4/5 inhibitor or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution, and ipatasertib should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored.

The lists of cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor *is available to advise* if questions arise regarding medications not listed above.

A11–4.2.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A11–4.2.3) may be used during the study at the discretion of the investigator.

A11–4.2.3 Prohibited Therapy for Atezo + Ipat Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined above in Section A11–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Quinidine or other anti-arrhythmic agents are prohibited.

  Stable doses of calcium-channel blockers are permitted.

  Stable doses of β-blockers, if an alternative treatment cannot be used, are permitted with caution.

A11–4.2.4 Prohibited Food for Atezo + Ipat Arm

Grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 10 days after the last dose of study ipatasertib.

A11–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + IPAT ARM

Contraception requirements for women and men in the Atezo + Ipat arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 28 days after the last dose of ipatasertib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A11–5 ASSESSMENT OF SAFETY FOR ATEZO + IPAT ARM

A11–5.1 SAFETY PLAN FOR ATEZO + IPAT ARM

The anticipated important safety risks are outlined below (see Sections A11–5.1.1, A11–5.1.2, and A11–5.1.3). Guidelines for management of patients who experience adverse events are provided in Section A11–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A11–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A11–5.1.2 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: diarrhea, nausea, vomiting, stomatitis/mucosal inflammation, erythema multiforme, asthenia, hyperglycemia, rash*, transaminase increased, dehydration, and decreased appetite*.

Refer to Section 6 of the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

A11–5.1.3 Risks Associated with Combination Use of Atezolizumab and Ipatasertib

On the basis of the frequency of adverse events associated with either atezolizumab or ipatasertib, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and ipatasertib: diarrhea, colitis, hepatotoxicity, rash, pneumonitis, and hyperglycemia.

A11–5.1.4 Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm

A11–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of ipatasertib can be reduced by 100 mg once a day (one-dose-level decrements) up to two times for management of drug-related toxicities (i.e., from 400 to 300 mg and then from 300 to 200 mg) as outlined in Table 4 below. If further dose reduction is indicated after two dose reductions for a specified drug-related adverse event, the patient must discontinue ipatasertib but may continue treatment with atezolizumab at the investigator's discretion. After dose reduction, the dose of ipatasertib may not be re-escalated.

Table 4 Suggested Dose Reductions for Ipatasertib

Dose Level	Ipatasertib
Starting dose	400 mg
First dose reduction	300 mg
Second dose reduction	200 mg
Third dose reduction	Discontinue

Note: After dose reduction, the dose of ipatasertib may not be re-escalated.

A11–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 5). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit.

Ipatasertib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 5). If ipatasertib is withheld for > 28 days, the patient will be discontinued from ipatasertib. If the investigator believes the patient is likely to derive clinical benefit, ipatasertib treatment can be resumed after being withheld for > 28 days. If corticosteroids are initiated for treatment of any toxicity, ipatasertib should be held and corticosteroids must be tapered to ≤ 10 mg/day oral prednisone or equivalent before ipatasertib can be resumed. *T*the investigator may determine the acceptable length of treatment interruption based on sound medical and

clinical judgment, taking into consideration the overall benefit/risk for the patient. *The Medical Monitor is available to advise as needed.*

If either atezolizumab or ipatasertib is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A11–4.1.2 for information on dose interruptions for reasons other than toxicity.

A11–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience adverse events are provided in Appendix 6 and Table 5, as outlined below:

- Appendix 6 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, pancreatic, neurologic, meningoencephalitis, and ocular events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Appendix 6 and that ipatasertib be withheld or discontinued per the guidelines in Table 5.
- Table 5 provides guidelines for the management of patients who experience the following potential overlapping toxicities: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table 5. For these potential overlapping toxicities, guidelines in Table 5 should be followed instead of guidelines in Appendix 6.
- Table 5 provides guidelines for the management of patients who experience adverse events associated with ipatasertib. It is recommended that atezolizumab and/or ipatasertib be withheld or discontinued per the guidelines in Table 5.

For cases in which management guidelines are not covered in Table 5 or Appendix 6, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reaction	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • Withhold ipatasertib. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and ipatasertib.
Gastrointestinal toxicity	
General guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or with dose hold of ipatasertib, a gastroenterologist should be consulted to rule out the risk of colitis and infection. Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
General guidance (cont.)	• Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: Medication — Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea, following the prophylactic dose of loperamide 4 mg initial daily dose (taken 2 mg twice a day or per local institutional standard), includes use of loperamide 2 mg after each loose watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. — Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid such as broth and Gatorade® drinks. — Dose reductions of ipatasertib will be by one level at a time (i.e., 400 to 300 mg; 300 to 200 mg) as outlined in Table 3. If Grade ≥ 2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued. Oral Supplementation — Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. — Consider rehydration therapy with oral electrolyte solution for Grade ≥ 1 diarrhea or vomiting. Dietary Modifications — Instruct patient to eat small meals and eliminate lactose-containing products from diet. — Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade).

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1	• Continue atezolizumab/placebo and ipatasertib. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to gastroenterologist for evaluation of possible colitis if appropriate. • Upon resolution, loperamide prophylaxis can be considered and continued as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.
Diarrhea, Grade 2	• Withhold atezolizumab and ipatasertib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to a gastroenterologist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one dose level for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continued as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 3	• Withhold ipatasertib and atezolizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to a gastroenterologist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab (at a fixed dose). If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 1	• Continue atezolizumab and ipatasertib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 5 days.
Colitis, Grade 2	• Withhold atezolizumab and ipatasertib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose ≤10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold atezolizumab and ipatasertib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose ≤10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines provided in Appendix 6. • Continue ipatasertib.
Symptomatic hypothyroidism	• Follow guidelines provided in Appendix 6. • Continue ipatasertib.
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Follow guidelines provided in Appendix 6. • Continue ipatasertib. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines provided in Appendix 6. • Continue ipatasertib. • For life-threatening immune-mediated hyperthyroidism, withhold ipatasertib. If event becomes clinically manageable within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in Appendix 6. • Continue ipatasertib.
Hyperglycemia, any grade	• All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects. • Workup should include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, HbA1C, C-peptide levels, anti-islet antibodies, and anti-GAD45 antibody. • Hyperglycemia should be treated per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia, Grade 1 Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue atezolizumab and ipatasertib. • The patient should receive education on a diabetic diet and consider home glucose monitoring. • Oral anti-diabetic medications (e.g., metformin) or insulin replacement may be started at the discretion of the investigator, guided by etiology of hyperglycemia.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Hyperglycemia, Grade 2 Fasting glucose value > 160 to 250 mg/dL (> 8.9–13.9 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to ≤ Grade 1 (≤ 160 mg/dL). • Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level. • If the patient previously has not been receiving any oral anti diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Hyperglycemia, Grade 3 Glucose value > 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting hyperglycemia resolves to ≤ Grade 1 (≤ 160 mg/dL) and contact Medical Monitor. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • The patient should adopt a diabetic diet and initiate home glucose monitoring. • If the patient is already on an oral anti-diabetic medication, ipatasertib should be reduced by one dose level when treatment is restarted. • If previously, the patient has not been receiving any oral anti diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If Grade 3 hyperglycemia recurs, the dose of ipatasertib should be reduced by one dose level when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Hyperglycemia, Grade 4 Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Withhold atezolizumab and ipatasertib dosing until fasting hyperglycemia resolves to ≤ Grade 1 (≤ 160 mg/dL) and contact Medical Monitor. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤160 mg/dL, reduce ipatasertib by one dose level when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib and atezolizumab and contact Medical Monitor.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Follow guidelines provided in Appendix 6. • Continue ipatasertib.
Hypophysitis (pan-hypopituitarism), Grade 4	• Follow guidelines provided in Appendix 6. • Withhold ipatasertib until Grade ≤ 2.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	• Continue atezolizumab and ipatasertib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab and ipatasertib.* • For recurrent pneumonitis, treat as a Grade 3 or 4 event.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*

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Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 2	• Withhold atezolizumab and ipatasertib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose ≤ 10 mg oral prednisone or equivalent, resume ipatasertib at current dose. • For recurrent events *or events with no improvement after 48-72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with *corticosteroids equivalent to* 1−2 mg/kg/day *IV methylprednisolone*. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab and ipatasertib.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-mediated events of > 5 days' duration:** • Consider withholding atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c]

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c]
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and ipatasertib. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 28 days and corticosteroid dose ≤ 10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib. • Permanently discontinue atezolizumab and ipatasertib for life-threatening hepatic events and contact the Medical Monitor.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c] • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month.
Dermatologic toxicity	
General guidance	• Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Antihistamine prophylaxis is strongly recommended for the first cycle, on the day before and the day of combination treatment (i.e., Days –1, 1, 14, and 15). For the second and subsequent atezolizumab infusions, antihistamine prophylaxis will be administered at the discretion of the investigator.
Dermatologic event, Grade 1	• Consider referring patient to a dermatologist. • Continue atezolizumab and ipatasertib. • Initiate supportive care (e.g., topical corticosteroids and continue antihistamine administration). • Consider treatment with 10 mg/day oral prednisone or equivalent.

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[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 2	• Consider referring patient to dermatologist for evaluation and perform a biopsy, if appropriate. • Continue topical corticosteroids and antihistamine administration. • Consider treatment with 10 mg/day oral prednisone or equivalent; treatment with higher steroid dose may be necessary as clinically indicated. • Ipatasertib: interrupt ipatasertib treatment until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. If steroid dose is ≤ 10 mg/day, ipatasertib may be resumed if clinically appropriate. • Atezolizumab: If steroid dose is ≤ 10 mg/day, atezolizumab should be continued.
Dermatologic event, Grade 3	• Withhold atezolizumab and ipatasertib. • Refer patient to dermatologist. Perform a biopsy if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent. • If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1–2 mg/kg/day. • Atezolizumab: if event resolves to Grade ≤ 1 within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. Only restart atezolizumab if steroid dose is ≤ 10 mg/day. [a, b, c] • Ipatasertib: if event resolves to Grade ≤ 1 or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level. Only restart ipatasertib if steroid dose is ≤ 10 mg/day. If not, permanently discontinue ipatasertib.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Withhold ipatasertib. • If event resolves to Grade 1 or better, resume ipatasertib. • Permanently discontinue ipatasertib if withheld for > 28 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Ipatasertib–related toxicities not described above	
Grade ≥ 3	• Withhold ipatasertib. Continue atezolizumab. • If the toxicity resolves to Grade 1 or better within 14 days, treatment with ipatasertib may be resumed at the prior dose level. • If the toxicity resolves to Grade 1 or better within 15 to 28 days, the dose of the ipatasertib should be reduced by one dose level. • Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes > 28 days, treatment with ipatasertib at a reduced dose may be resumed, or ipatasertib may be permanently discontinued, at the discretion of the investigator

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Ipat Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 3	• Follow guidelines provided in Appendix 6. • Withhold ipatasertib. • If event resolves to Grade 1 or baseline within 28 days and corticosteroid dose ≤ 10 mg oral prednisone or equivalent, resume ipatasertib. If not, permanently discontinue ipatasertib.
Grade 4	• Follow guidelines provided in Appendix 6. • Withhold ipatasertib. • If event resolves to Grade 1 or baseline within 28 days and corticosteroid dose ≤ 10 mg oral prednisone or equivalent, resume ipatasertib. If not, permanently discontinue ipatasertib.

Atezo + Ipat = atezolizumab plus ipatasertib; BAL = bronchoscopic alveolar lavage; *CRS = cytokine-release syndrome;* GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; ULN = upper limit of normal.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A11–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + IPAT ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Ipat arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Vasculitis

- Grade ≥ 2 rash
- Grade ≥ 3 diarrhea or Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management.
- Grade ≥ 3 hyperglycemia
- Any grade acute coronary syndrome or myocardial infarction

A11–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + IPAT ARM

A11–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of ipatasertib and 5 months after the last dose of atezolizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A11–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the last dose of ipatasertib. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant

partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A11–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A11–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A11–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + IPAT ARM

Table 6 Schedule of Activities Atezo + Ipat Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs [e]		x	x	x	x	x	
Weight [f]		x		x		x	
Complete physical examination [g]						x	
Limited physical examination [f, h]		x	x	x	x		
ECOG Performance Status [f]		x		x		x	
ECG [f, i]		Perform as clinically indicated					
Hematology [j]		x [k]	x	x	x	x	
Chemistry [l, m]		x [k,]	x	x	x	x	
Coagulation (INR and aPTT)		x [k]	x	x	x	x	
Fasting lipid panel and HbA_{1c} [n]		x [k]				x	
TSH, free T3 (or total T3), free T4 [o]		x [k]				x	
Pregnancy test [p]		x [k]		x		x	x [p]
Blood sample for blood-based NGS ctDNA test						x	
Urinalysis [q]		Perform as clinically indicated					

Table 6 Schedule of Activities Atezo + Ipat Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (28-day cycles) [a]				Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up [d]
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months (±7 days)
Serum autoantibody sample [r]	See Appendix 2	Perform if a patient experiences a suspected immune-mediated adverse event					
PK samples		Refer to Table 7 below					
ADA samples		Refer to Table 7 below					
Biomarker samples		Refer to Table 7 below					
Blood sample for RBR (optional) [s]		x					
Tumor biopsy		x [t]					
Tumor biopsy (optional)		x [u]					
Tumor response assessments		x [v, w, x]					
Concomitant medications [y]		x	x	x	x	x	
Adverse events [z]		x	x	x	x	x [z]	x [z]
Dispense ipatasertib [aa, bb]		x		x			
Study drug accountability [cc]				x			
Atezolizumab administration [aa, dd]		x	x	x	x		
Prophylaxis anti-diarrheal		x [ee, ff]		x [ee, ff]			
Survival follow-up and anti-cancer treatment							x [gg]

Table 6 Schedule of Activities Atezo + Ipat Arm (cont.)

ADA = anti-drug antibody; Atezo + Ipat = atezolizumab plus ipatasertib; BID = twice a day; CT = computed tomography; ctDNA = circulating tumor DNA; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; NGS = next-generation sequencing; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Screen.=screening; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) or unacceptable toxicity to ipatasertib will be given the option of receiving a different treatment combination in Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Table 6 Schedule of Activities Atezo + Ipat Arm (cont.)

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), CPK, sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. CPK will be performed only on Day 1 of each cycle and at treatment discontinuation. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] A fasting chemistry panel (performed after ≥ 8 hr of fasting) is required on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and at treatment discontinuation. A non-fasting chemistry panel can be performed on Day 15 of Cycles ≥ 3.

[n] Fasting lipid panel (cholesterol, HDL, LDL, and triglyceride) and HbA_{1c} will be assessed (after ≥ 8 hr of fasting) on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[o] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[p] All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[t] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[u] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible and may undergo additional on-treatment biopsies at any other time during Stage 1 or Stage 2 at the investigator's discretion.

Table 6 Schedule of Activities Atezo + Ipat Arm (cont.)

[v] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[w] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[x] For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[z] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[aa] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

Table 6 Schedule of Activities Atezo + Ipat Arm (cont.)

[bb] All patients will receive ipatasertib at a dose of 400 mg orally once a day on Days 1–21 of each 28-day cycle. Ipatasertib should be taken approximately at the same time each day and no earlier or later than 4 hours from the scheduled time. If ipatasertib treatment is withheld because of toxicity, the patient is encouraged, at the discretion of the investigator, to make up the missed doses during the 7 days-off week for ipatasertib, so that 21 daily doses in every 28 days is maintained.

[cc] In order to assess the actual intake of ipatasertib and of anti-diarrheal medication use, patients should complete a medication diary each day. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed anti-diarrheal medications, including the recommended dosage and route of administration (see Section A11–4.1.2.1 for details). Patients should use the diary to record daily ipatasertib dosing and specifically any anti-diarrheal used (prescribed or over the counter) taken on that cycle of treatment.

[dd] Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A11–4.1.2.2 for details on atezolizumab infusions (including measurement of vital signs).

[ee] Loperamide 2 mg BID or equivalent or per local institutional guideline for the first cycle. If loose watery stools occur, take additional 2 mg after each loose watery stool and up to 16 mg per day.

[ff] If side effects are not tolerated, doses may be reduced (see Table 4). After 1 cycle without any diarrhea, continuation is at physician's discretion. If diarrhea occurs, it should be managed per guidelines in Table 5; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.

[gg] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Patients Treated with Atezo + Ipat

Visit	Time	Sample
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to study treatment	• Ipatasertib PK (plasma) [a] • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
	Between 1 and 3 hours after ipatasertib dose	• Ipatasertib PK (plasma) [a]
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo + Ipat = atezolizumab plus ipatasertib; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Ipatasertib and its metabolite(s) will be tested.

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Appendix 12
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A12–1 BACKGROUND ON ATEZO + SG ARM

A12–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab (Tecentriq®) is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, hepatocellular carcinoma, and melanoma. Atezolizumab is also approved in combination with nab-paclitaxel for the treatment of patients with PD-L1–positive triple-negative breast cancer (TNBC).

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A12–1.2 BACKGROUND ON SACITUZUMAB GOVITECAN

Sacituzumab govitecan is a trophoblast cell-surface antigen 2 (TROP-2)-directed antibody–drug conjugate (ADC) consisting of three components: 1) a humanized IgG1κ monoclonal antibody hRS7, which binds to TROP-2; 2) SN-38, a topoisomerase I inhibitor and active metabolite of irinotecan; and 3) a proprietary hydrolyzable linker (CL2A) that couples hRS7 to SN-38.

TROP-2 is a transmembrane calcium signal transducer glycoprotein of the tumor-associated calcium signal transducer gene family that is expressed in many tumors. Pharmacology data suggest that sacituzumab govitecan binds to TROP-2–expressing cancer cells and undergoes internalization with the subsequent release of SN-38 via hydrolysis of the linker. Upon release, SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I–induced single-stranded DNA breaks, resulting in DNA damage that leads to apoptosis and cell death.

The hydrolyzable linker of sacituzumab govitecan may also permit release of SN-38 in the acidic microenvironment of the tumor without TROP-2 binding.

Sacituzumab govitecan has shown anti-tumor activity in nonclinical and clinical studies and was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with metastatic TNBC who have received at least 2 prior therapies for metastatic disease and fast track designation for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (FDA 2020).

Refer to the Sacituzumab Govitecan Investigator's Brochure for details on nonclinical and clinical studies.

A12–2 RATIONALE FOR ATEZO + SG ARM

A12–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors (CPIs), have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the

remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A12–2.2 TARGETING TROP-2

TROP-2 is a cell-surface marker of trophoblast cells that is expressed in many solid tumors at higher levels compared with normal tissue. TROP-2 binds several cellular proteins, including insulin-like growth factor-1, claudin-1, claudin-7, cyclin D1, and protein kinase C, and has been implicated in the regulation of tumor growth, invasion, and spread. Through activation of the ERK1/2-mitogen-activated protein kinase (MAPK) pathway, TROP-2 also contributes to cell cycle progression and could play a role in stem-cell biology through deregulation of stem-cell functions via the Notch, Hedgehog, and Wnt pathways.

Overexpression of TROP-2 has been reported in most human epithelial cancers, including oral, head and neck, thyroid, lung, esophageal, gastric, colorectal, pancreatic, breast, renal, uterine, cervical, ovarian, and glioma (Goldenberg et al. 2018). Therapeutic targeting of TROP-2 may therefore be a promising treatment for patients across a wide spectrum of malignancies. However, the predictive value of TROP-2 expression remains unclear because of the absence of a control arm and the lack of a clear association between tumor TROP-2 expression per immunohistochemistry (IHC) and efficacy in patients with NSCLC (Heist et al. 2017). In addition, the utility of TROP-2 as biomarker for selection of patients with NSCLC for sacituzumab govitecan is not clear because of the high prevalence of TROP-2 expression in NSCLC, ranging from 64% (high expression per IHC, non-squamous NSCLC) and 75% (high expression per IHC, squamous NSCLC) (Inamura et al. 2017) to 80% (high expression per IHC, non-squamous NSCLC) and 100% (high expression per IHC, squamous NSCLC) (Omori et al. 2019).

A12–2.3 BENEFIT–RISK ASSESSMENT

A Phase I study of sacituzumab govitecan in advanced solid cancers, including NSCLC, showed encouraging therapeutic activity (Starodub et al. 2015). Recent data from a single-arm study of sacituzumab govitecan in patients with NSCLC, showed an objective response rate of 19% among the 47 enrolled patients, with a median response duration of 6 months, and a clinical benefit rate (complete response + partial response + stable disease $\geq$ 4 months) of 43%, a median progression-free survival of 5.2 months, and a median overall survival of 9.5 months. Five (36%) of 14 patients who received CPIs showed tumor shrinkage, including two (14%) with partial response (Heist et al. 2017). Combining sacituzumab govitecan, an ADC that can cause tumor-cell death with possible neoantigen release, with atezolizumab, an immune-stimulating agent, could have synergistic effects and have promising therapeutic potential in CPI-experienced NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A12–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + SG ARM

A12–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab.

A12–3.2 RATIONALE FOR SACITUZUMAB GOVITECAN DOSE AND SCHEDULE

Sacituzumab govitecan will be administered at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle, which is an approved dosage for sacituzumab govitecan. Additional safety and efficacy information can be found in the Sacituzumab Govitecan Investigator's Brochure.

A12–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + SG ARM

A12–4.1 TREATMENT IN ATEZO + SG ARM

A12–4.1.1 Formulation, Packaging, and Handling

A12–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A12–4.1.1.2 Sacituzumab Govitecan

Sacituzumab govitecan will be supplied by the Sponsor as a sterile, off-white to yellowish lyophilized powder in a single-dose glass vial. The vial contains approximately 200 mg of sacituzumab govitecan for reconstitution.

For information on the formulation and handling of sacituzumab govitecan, see the pharmacy manual.

A12–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + SG arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary

to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + SG Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Sacituzumab govitecan 10 mg/kg by IV infusion on Days 1 and 8 [a] • Atezolizumab 1200 mg by IV infusion on Day 1 [b]

Atezo + SG = atezolizumab plus sacituzumab govitecan.

[a] There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[b] The atezolizumab infusion should be initiated approximately 60 minutes following completion of the sacituzumab govitecan infusion.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or sacituzumab govitecan are available.

Sacituzumab govitecan doses in excess of the recommended dose may be associated with exposure-related toxicities, such as neutropenia and diarrhea. These toxicities, frequently associated with chemotherapies, should be managed through supportive care to prevent serious consequences (such as dehydration and infection) and provide symptomatic relief, in accordance with institutional guidelines.

A12–4.1.2.1 Sacituzumab Govitecan

Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Days 1 and 8 of each 21-day cycle.

Administration of sacituzumab govitecan will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions (IRRs).

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion. Prior to each dose of sacituzumab govitecan, premedication for prevention of IRRs and prevention of chemotherapy-induced nausea and vomiting is recommended.

Premedicate with antipyretics, H_1, and H_2 blockers prior to infusion; corticosteroids may be used for patients who have had prior IRRs.

Premedicate with a two- or three-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist), as well as other drugs as indicated.

Refer to the pharmacy manuals for detailed instructions on drug preparation, storage, and administration.

Guidelines for the medical management of IRRs for sacituzumab govitecan are provided in Section A12–5.1.4.

Guidelines for sacituzumab govitecan treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4. Sacituzumab govitecan treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A12–4.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Atezolizumab should be administered approximately 60 minutes after completion of the sacituzumab govitecan infusion.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15 minutes. • If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of IRRs for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A12–5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A12–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to sacituzumab govitecan will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 3, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + SG Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; SG = sacituzumab govitecan; Lina = linagliptin.

Refer to Appendix 16 and Appendix 17 for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A12–4.2 CONCOMITANT THERAPY FOR ATEZO + SG ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A12–4.2.1 Permitted Therapy for Atezo + SG Arm

Patients are permitted to use the following therapies during the study:

- Colony-stimulating factors (CSFs), such as granulocyte colony-stimulating factors (G-CSFs) and erythropoiesis-stimulating agents (ESAs), which are to be administered per local practice/institutional guidelines or the American Society of Clinical Oncology guidelines for hematopoietic CSFs (Smith et al. 2015) and American Society of Clinical Oncology/American Society of Hematology guidelines for ESAs (Bohlius et al. 2019)
- Oral contraceptives
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A12–4.2.3).
- Mineralocorticoids (e.g., fludrocortisone)

- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Bisphosphonates and denosumab for the prevention of skeletal events
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Treatment with atezolizumab and sacituzumab govitecan may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anti-convulsant therapy, if required, is administered at a stable dose.

  Treatment with atezolizumab may be continued during radiotherapy. Treatment with sacituzumab govitecan should be withheld for 1 week prior to radiotherapy and for 2 weeks after radiotherapy.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious

infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence on potential interactions of COVID-19 vaccines with sacituzumab govitecan. Based on the mechanism of action of sacituzumab govitecan, no potential interaction with COVID-19 vaccines is expected. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A12–4.2.2 Cautionary Therapy for Atezo + SG Arm

A12–4.2.2.1 Corticosteroids and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section A12–5.1.4 for guidelines for managing specific adverse events).

A12–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A12–4.2.3) may be used during the study at the discretion of the investigator.

A12–4.2.3 Prohibited Therapy for Atezo + SG Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of

palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A12–4.2.1.

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Strong inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) should be avoided during study treatment because these agents could potentially increase the risk for neutropenia
- Strong inducers of UGT1A1 should be avoided during study treatment because these agents could decrease exposure to sacituzumab govitecan

A12–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + SG ARM

Contraception requirements for women and men in the Atezo + SG arm are outlined below:

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab and for 6 months after the last dose of sacituzumab govitecan.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 3 months after the last dose of sacituzumab govitecan. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 3 months after the last dose of sacituzumab govitecan to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A12–5 ASSESSMENT OF SAFETY FOR ATEZO + SG ARM

A12–5.1 SAFETY PLAN FOR ATEZO + SG ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and sacituzumab govitecan in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A12–5.1.1, A12–5.1.2, and A12–5.1.3). Guidelines for management of patients who experience adverse events are provided in Section A12–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Because of the potential for overlapping toxicities, a minimum of 6 patients in the Atezo + SG arm must complete a safety evaluation before additional patients can be enrolled in that arm. Administration of atezolizumab and sacituzumab govitecan will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A12–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6

of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A12–5.1.2 Risks Associated with Sacituzumab Govitecan

Sacituzumab govitecan has been associated with risks such as the following: IRRs, gastrointestinal toxicities, infectious toxicities (may involve sepsis, pneumonia), fatigue, and hematologic toxicities. Patients who are homozygous for the UGT1A1*28 allele are potentially at increased risk for neutropenia, febrile neutropenia, diarrhea, and anemia and may be at increased risk for other adverse events following initiation of sacituzumab govitecan treatment. Additional monitoring may be required in those patients. Refer to Section 6 of Sacituzumab Govitecan Investigator's Brochure for a detailed description of anticipated risks for sacituzumab govitecan.

A12–5.1.3 Risks Associated with Combination Use of Atezolizumab and Sacituzumab Govitecan

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and sacituzumab govitecan: gastrointestinal events, dermatologic events, and hepatic events.

A12–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + SG Arm

A12–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

For management of drug-related toxicities, the dose of sacituzumab govitecan can be reduced by 2.5 mg/kg (i.e., one dose level) up to two times, as outlined in Table 4.

Table 4 Suggested Dose Reductions for Sacituzumab Govitecan

	Initial Dose	First Dose Reduction	Second Dose Reduction
Sacituzumab govitecan	10 mg/kg	7.5 mg/kg	5 mg/kg

If further dose reduction is indicated for sacituzumab govitecan after two dose reductions, sacituzumab govitecan should be discontinued. After dose reduction, the dose of sacituzumab govitecan may not be escalated.

A12–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for more than 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for more than 12 weeks to allow for patients to

taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for more than 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Sacituzumab govitecan treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If toxicity related to sacituzumab govitecan prevents dose resumption for more than 3 weeks after interrupting treatment, the patient will be discontinued from sacituzumab govitecan. Sacituzumab govitecan can be resumed after being withheld for more than 3 weeks if the investigator and the patient is likely to derive clinical benefit. If either atezolizumab or sacituzumab govitecan is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with sacituzumab govitecan or atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A12–4.1.2 for information on dose interruptions for reasons other than toxicity (e.g., surgical procedures).

A12–5.1.4.3 Management Guidelines for Adverse Events

Patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) on Day 1 or each cycle and an ANC of $\geq 1.0 \times 10^9$/L (1000/μL) on Day 8 of each cycle to receive treatment with sacituzumab govitecan. Guidelines for management of hematologic toxicities and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table 5. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit–risk balance when managing individual cases.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm

Event	Action to Be Taken
IRRs, *CRS,* and anaphylaxis	
General guidelines	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • Guidelines for management of IRRs for sacituzumab govitecan are provided below. • For anaphylaxis precautions, see Appendix 5.
IRR to sacituzumab govitecan, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
IRRs, *CRS,* and anaphylaxis (cont.)	
IRR to sacituzumab govitecan, Grade 2 *or 3*	• Interrupt infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for IRRs. Corticosteroids may be used for patients who have had prior infusion reactions. • For recurrent Grade 2 *or Grade 3* IRRs that fail to recover within 6 hours despite optimal management, sacituzumab govitecan should be permanently discontinued.
IRR to sacituzumab govitecan, Grade 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
IRRs, *CRS,* and anaphylaxis (cont.)	
Hemophagocytic lymphohistiocytosis or macrophage activation syndrome	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan and contact Medical Monitor for guidance.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
General guidelines	• *General guidance for managing gastrointestinal events of all grades is provided below, followed by grade-specific management guidelines.* • Because nausea, vomiting, and diarrhea are frequent sacituzumab govitecan–associated toxicities that potentially overlap with atezolizumab-associated toxicities, appropriate treatment, including fluid and electrolyte replacement (as needed), is required to minimize the risk of serious consequences, such as dehydration. <u>Diarrhea</u> • Dietary modification should be recommended for the management of diarrhea, including adequate fluid intake to maintain hydration. • Administer antibiotics as clinically indicated. • For excessive cholinergic responses to study treatment (e.g., abdominal cramping, diarrhea, salivation), administer appropriate premedication (e.g., atropine) for subsequent treatments.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
General guidelines	Nausea and Vomiting • Because sacituzumab govitecan is considered to be moderately emetogenic, premedication with a two- or three-drug anti-emetic regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK1 receptor antagonist, as well as other drugs as indicated) should be administered prior to sacituzumab govitecan. • If nausea and vomiting are persistent, a three-drug regimen, including a 5-HT3 inhibitor (ondansetron or palonosetron, or other agents according to local practices), an NK1-receptor antagonist (fosaprepitant or aprepitant), and dexamethasone (10 mg PO or IV), may be administered. Anticipatory nausea can be treated with olanzapine.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. – If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. – If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines. • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • Treat with IV fluids and consider hospitalization. • Initiate symptomatic treatment such as the following: – Loperamide can be administered at the onset of treatment-related diarrhea (after infectious causes are ruled out) at an initial dose of 4 mg, followed by 2 mg with every episode of diarrhea to a maximum dose of 16 mg/day. – If diarrhea is not resolved after 24 hours, consider adding diphenoxylate/atropine and/or opium tincture, as clinically indicated. – If diarrhea persists, consider adding octreotide 100–150 μg SC three times per day, or treat as per institutional guidelines.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 3 or 4 (cont.)	• First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-diarrheal agents. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Nausea or vomiting, Grade 1 or 2	• *Refer to general guidelines for managing nausea and vomiting.*
Nausea or vomiting, Grade 3	• Continue atezolizumab. For persistent nausea that does not respond to treatment and for all vomiting events, withhold sacituzumab govitecan. • Manage per institutional guidelines. • First and second occurrence: If sacituzumab govitecan is withheld and event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with anti-emetics. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Nausea or vomiting, Grade 4	• Withhold atezolizumab and sacituzumab govitecan. • Manage per institutional guidelines. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab. [a] • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan; reduce the dose by one level if event does not resolve within 1 week after interrupting treatment and is not manageable with antiemetics. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia	
General guidelines	• *General guidance for managing neutropenia of all grades is provided below, followed by grade-specific management guidelines.* • Sacituzumab govitecan should only be administered if Day 1 ANC $\geq 1.5 \times 10^9$/L (1500/μL) and Day 8 ANC $\geq 1.0 \times 10^9$/L (1000/μL). • The routine prophylactic use of growth factors is not required; however, prophylactic administration may be considered and should comply with American Society of Clinical Oncology guidelines. Growth factors may be administered to patients who have experienced febrile neutropenia or Grade 3 or Grade 4 neutropenia and to patients at high risk of poor clinical outcomes, including those with prolonged neutropenia, ANC $< 0.1 \times 10^9$/L (100/μL), febrile neutropenia, or serious infections.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia (cont.)	
Neutropenia, Grade 3 or 4	• Withhold atezolizumab and sacituzumab govitecan. • At first occurrence, initiate G-CSF prophylaxis for subsequent dosing. • If event resolves to Grade 2 or better within 12 weeks after event onset, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a] **Grade 4 neutropenia lasting ≥7 days, febrile neutropenia, or neutropenia that delayed dosing by 2–3 weeks:** • First occurrence: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a] • Second and third occurrence: If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Fourth occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Neutropenia (cont.)	
Neutropenia, Grade 3 or 4 (cont.)	**All other cases of Grade 3 or 4 neutropenia:** If event resolves to Grade 1 or better (Day 1) or to Grade 2 or better (Day 8) within 3 weeks after interrupting treatment, resume sacituzumab govitecan. b If not, permanently discontinue sacituzumab govitecan, contact the medical monitor and refer the patient to a hematologist for further investigations.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. **Event that has delayed treatment by 2–3 weeks or event that persists for ≥48 hours despite optimal medical management:** • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a] **All other Grade 3 events:** • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Dermatologic events (cont.)	
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • If event resolves to Grade 1 or better, resume sacituzumab govitecan. • Permanently discontinue sacituzumab govitecan if withheld for > 3 weeks or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin ≤ 2 × ULN	• Continue atezolizumab and sacituzumab govitecan.
AST/ALT > 3 × ULN to 5 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and sacituzumab govitecan. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-mediated events of > 5 days' duration:** • Consider withholding atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and contact Medical Monitor. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab. Withhold sacituzumab govitecan. • If event resolves to AST/ALT ≤ 3 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. If not, permanently discontinue sacituzumab govitecan. [a] • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN (cont.)	**Suspected immune-mediated events:** • Withhold atezolizumab and sacituzumab govitecan. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a] • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN with 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and sacituzumab govitecan and contact Medical Monitor. [a]
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.

Atezo + SG = atezolizumab plus sacituzumab govitecan; *CRS = cytokine-release syndrome;* G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 3 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN while within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN within 12 weeks after event onset, resume atezolizumab. [d, e] If not, permanently discontinue atezolizumab and contact Medical Monitor. [a] • Permanently discontinue atezolizumab and sacituzumab govitecan for life-threatening hepatic events and contact the Medical Monitor.

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin (cont.)	
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] Withhold sacituzumab govitecan. • Monitor LFTs every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN, taper corticosteroids over ≥1 month. • If event resolves to AST/ALT ≤3 × ULN with total bilirubin ≤2 × ULN within 3 weeks after interrupting treatment, resume sacituzumab govitecan with dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Endocrine events	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Withhold sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Endocrine events (cont.)	
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Withhold sacituzumab govitecan. • When symptoms are controlled and thyroid function is improving, resume sacituzumab govitecan. [b]

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Sacituzumab govitecan–related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab and sacituzumab govitecan.
Grade 3	• Continue atezolizumab. Withhold sacituzumab govitecan. **Toxicity that has delayed treatment by 2–3 weeks or non-hematologic toxicity that persists for ≥48 hours despite optimal medical management:** • First and second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a] **All other Grade 3 toxicities:** • If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Sacituzumab govitecan–related toxicities not described above (cont.)	
Grade 4	• Withhold atezolizumab and sacituzumab govitecan. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. **Toxicity that has delayed treatment by 1–3 weeks or non-hematologic toxicity:** • First occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by one level, e.g., from 10 mg/kg to 7.5 mg/kg. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Second occurrence: If event resolves to Grade 1 or better within 3 weeks after interrupting treatment, resume sacituzumab govitecan with the dose reduced by two levels, e.g., from 10 mg/kg to 5 mg/kg. [b, c] If not, permanently discontinue sacituzumab govitecan. [a] • Third occurrence: Permanently discontinue sacituzumab govitecan and contact Medical Monitor. [a] **All other Grade 4 toxicities:** • If event resolves to Grade 1 or better while within 3 weeks after interrupting treatment, resume sacituzumab govitecan. [b] If not, permanently discontinue sacituzumab govitecan. [a]

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + SG Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue sacituzumab govitecan.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Sacituzumab govitecan may continued at the discretion of the investigator per medical judgment.

Atezo + SG = atezolizumab plus sacituzumab govitecan; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LFT = liver function test; PO = by mouth; ULN = upper limit of normal.

[a] Resumption of treatment may be considered if the investigator believes the patient is likely to derive clinical benefit. *The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If the event has not resolved within 1 week, the dose should be skipped. There should be a minimum of 7 days between the Day 1 and Day 8 infusions and a minimum of 14 days between the Day 8 infusion and the Day 1 infusion of the next cycle.

[c] The dose of sacituzumab govitecan may be reduced from 10 mg/kg to 7.5 mg/kg (one dose level) and then from 7.5 mg/kg to 5 mg/kg (one dose level) (see Section A12–5.1.4.1 for details).

[d] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[e] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

A12–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + SG ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + SG arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A12–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + SG ARM

A12–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or within 6 months after the last dose of sacituzumab govitecan. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A12–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of sacituzumab govitecan. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A12–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A12–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A12–6 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + SG ARM

Table 6 Schedule of Activities for Patients Treated with Atezo + SG

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) [a]				Stage 2 Screen. (see Appendix 2) or Treatment Discontinuation [d]	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 8 [c]	Day 1 [c]	Day 8 [c]		Every 3 Months
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available					
Vital signs [e]		x		x		x	
Weight [f]		x		x		x	
Complete physical examination [g]						x	
Limited physical examination [f, h]		x	x	x	x		
ECOG Performance Status [f]		x		x		x	
ECG [f, i]		Perform as clinically indicated				x	
Hematology [j, k]		x	x	x	x	x	
Chemistry [k, l]		x	x	x	x	x	
Coagulation (INR and aPTT)		Perform as clinically indicated				x	
TSH, free T3 (or total T3), free T4 [m]		x [k, m]				x	
Pregnancy test [k, n]		x		x		x	x [n]
Blood sample for blood-based NGS ctDNA test						x	
Urinalysis [o]		Perform as clinically indicated					
Serum autoantibody sample [p]		Perform if a patient experiences a suspected immune-mediated adverse event					

Table 6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-day cycles) [a]				Stage 2 Screen. (see Appendix 2) or Treatment Discontinuation [d]	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2			
	Day –28 to –1	Day 1	Day 8 [c]	Day 1 [c]	Day 8 [c]		Every 3 Months
PK sample	See Appendix 2	Refer to Table 7					
ADA sample		Refer to Table 7					
Biomarker samples		Refer to Table 7					
Blood sample for RBR (optional) [q]		x					
Tumor biopsy		x [r]					
Tumor biopsy (optional)		x [s]					
Tumor response assessments		x [t, u, v]					
Concomitant medications [w]		x	x	x	x	x	
Adverse events [x]		x	x	x	x	x [x]	x [x]
Sacituzumab govitecan administration [y, z]		x	x	x	x		
Atezolizumab administration [y, aa]		x		x			
Survival follow-up and anti-cancer treatment							x [bb]

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; NGS = next-generation sequencing; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

Table 6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Visits can occur up to 2 days after the scheduled visit day.

[d] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.1 for details) may be used as the treatment discontinuation visit.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion of each drug. For subsequent infusions of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion of each drug and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] If screening laboratory assessment are performed within 96 hours before Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[n] All women of childbearing potential will have a urine or serum pregnancy test performed at specified visits during treatment and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Table 6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

[p] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[q] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[r] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have granted approval for mandatory serial biopsies (see Section 3.1.2) will also undergo tumor biopsy sample collection at Week 4 (±7 days) (if deemed clinically feasible by the investigator). See Section 4.5.7 for tissue sample requirements.

[s] Patients who consent to optional biopsies will undergo tumor biopsy sample collection 4 weeks (± 7 days) after treatment initiation, if deemed clinically feasible, and may undergo additional on-treatment biopsies at any other time during the study at the investigator's discretion.

[t] Patients will undergo tumor assessments at baseline, every 6 weeks (± 1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (± 2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1 with the following exceptions: 1) atezolizumab-treated patients who continue treatment after radiographic disease progression will undergo tumor assessments every 6 weeks (± 1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), and 2) patients with bone metastases will have bone scans every 12 weeks (± 1 week for the first 48 weeks, and ± 2 weeks thereafter). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[u] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the tumor assessment schedule described above (see footnote “s”). Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[v] For patients who undergo screening for Stage 2: Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

Table 6 Schedule of Activities for Patients Treated with Atezo + SG (cont.)

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[x] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[y] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[z] Sacituzumab govitecan will be administered by IV infusion at a dose of 10 mg/kg on Day 1 and 8 of each 21-day cycle. Sacituzumab govitecan should be administered prior to the atezolizumab infusion. Sacituzumab govitecan should be infused over approximately 3 hours on first infusion and over 1 hour on subsequent infusions, if the first infusion is well tolerated.

[aa] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Refer to Section A12–4.1.2.2 for details on atezolizumab infusions (including measurement of vital signs).

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 8 of Cycle 1	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)
Day 8 of Cycle 3	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 5	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)
Day 1 of Cycle 7	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested along with sacituzumab govitecan PK.

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + SG Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 9	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)
Day 1 of Cycle 11 and every third cycle thereafter (e.g., Cycles 14, 17, 20, etc.)	Prior to study treatment	• Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum)
	30 minutes after sacituzumab govitecan infusion	• Sacituzumab govitecan PK[a] (serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Sacituzumab govitecan PK[a] (serum) • Sacituzumab govitecan ADA (serum) • Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + SG = atezolizumab plus sacituzumab govitecan; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] Total antibody, free SN-38, SN-38 glucuronide, and total SN-38 will be tested along with sacituzumab govitecan PK.

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Appendix 13
Placeholder for Future Arm

The atezolizumab plus CPI-444 arm has been removed, as all randomized patients have completed treatment and follow-up. The content of Appendix 13 (previously entitled "Study Details Specific to Atezo + CPI-444 Arm") has been deleted. Appendix 13 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 14
Study Details Specific to the Atezo + Pem + Carbo Arm

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A14–1 BACKGROUND ON ATEZO + PEM + CARBO ARM

A14–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 ([B7-1] also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A14–1.2 BACKGROUND ON PEMETREXED AND CARBOPLATIN IN NON–SMALL CELL LUNG CANCER

Standard of care for first-line treatment of non-squamous NSCLC that does not harbor a driver mutation is a platinum doublet consisting of either cisplatin or carboplatin in combination with a taxane or pemetrexed, with or without bevacizumab. Furthermore, in a Phase III clinical study evaluating pemetrexed maintenance therapy compared with placebo following four cycles of platinum-based doublet chemotherapy, pemetrexed significantly improved progression-free survival (4.3 vs. 2.6 months) (hazard ratio

[HR] = 0.50; 95% CI: 0.42, 0.61; p < 0.0001) and overall survival (OS; 13.4 vs. 10.6 months) (HR = 0.79; 95% CI: 0.65, 0.95; p = 0.012) (Ciuleanu et al. 2009). This Phase III trial resulted in regulatory approval for pemetrexed as maintenance therapy for patients with locally advanced or metastatic non-squamous NSCLC whose disease had not progressed after four cycles of platinum-based first-line chemotherapy.

A14–2 RATIONALE FOR ATEZO + PEM + CARBO ARM

A14–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A14–2.2 RATIONALE FOR COMBINING IMMUNE CHECKPOINT INHIBITORS WITH CHEMOTHERAPY

Tumor-cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable this hypothesis to be tested.

Pembrolizumab, a PD-1 inhibitor, has been approved in combination with pemetrexed and carboplatin for the first-line treatment of metastatic non-squamous NSCLC, irrespective of PD-L1 expression. The objective response rate (ORR) for pembrolizumab in combination with pemetrexed and carboplatin (55%; 33 of 60 patients) was nearly double the ORR for pemetrexed and carboplatin alone (29%; 18 of 63 patients). In addition, 92% of patients treated with pembrolizumab plus chemotherapy had a duration of response of 6 months or more, compared with 81% of patients treated with chemotherapy alone. Median PFS was 13.0 months for patients treated with pembrolizumab plus chemotherapy and 8.9 months for patients treated with chemotherapy alone (Langer et al. 2016). The incidence of Grade 3 or higher treatment-related adverse events was similar between groups.

As of 10 February 2015 (data cutoff) in an ongoing Phase Ib study of first-line treatment of NSCLC (Study GP28328), the ORR was 70.6% (12 of 17) for patients treated with atezolizumab plus pemetrexed and carboplatin. Atezolizumab in combination with chemotherapy was not associated with additive severe (Grade 3 or higher) toxicities. The adverse events observed for atezolizumab in combination with chemotherapy were consistent with the known risks of each study treatment. Detailed clinical study results for Study GP28328 can be found in the Atezolizumab Investigator's Brochure.

A14–2.3 BENEFIT–RISK ASSESSMENT

The efficacy and safety results for pembrolizumab plus chemotherapy (Langer et al. 2016) and the preliminary efficacy and safety results for atezolizumab plus chemotherapy (Study GP28328) offer evidence of an acceptable safety profile and a promising therapeutic potential when combining a PD-1 or PD-L1 inhibitor with pemetrexed and carboplatin as treatment for NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A14–3 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A14–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + PEM + CARBO ARM

A14–4.1 TREATMENT IN ATEZO + PEM + CARBO ARM

A14–4.1.1 Formulation, Packaging, and Handling

A14–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A14–4.1.1.2 Pemetrexed and Carboplatin

For information on the formulation, packaging, and handling of pemetrexed and carboplatin, refer to the local prescribing information for each agent.

A14–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus pemetrexed plus carboplatin (Atezo + Pem + Carbo) arm will receive treatment as outlined in Table 1. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). Patients will continue pemetrexed until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Carboplatin will be administered for the first four or six cycles, depending on local clinical practice. However, carboplatin will be discontinued for patients who experience unacceptable toxicity or disease progression per RECIST v1.1. It is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table 1 Treatment Regimen for Atezo + Pem + Carbo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Pemetrexed 500 mg/m^2 IV on Day 1 of each cycle • Carboplatin AUC 6 mg/mL/min (Calvert formula dosing) IV on Day 1 of the first four or six cycles

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available. For information on overdosing of pemetrexed or carboplatin, refer to the local prescribing information for each agent.

A14–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.5. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A14–4.1.2.2 Pemetrexed and Carboplatin Administration

Pemetrexed will be administered by IV infusion at a dose of 500 mg/m^2 over 10 minutes on Day 1 of each 21-day cycle. Carboplatin will be administered by IV infusion to achieve an initial target area under the concentration–time curve (AUC) of 6 mg/mL/min (Calvert formula dosing) over 30–60 minutes on Day 1 of the first four or six cycles, depending on local clinical practice. Pemetrexed will be administered approximately 30 minutes after completion of the atezolizumab infusion, and carboplatin will be administered approximately 30 minutes after completion of the pemetrexed infusion.

Patients should receive corticosteroid, folic acid, and vitamin B-12 premedication for pemetrexed according to the local standard of care and manufacturer's instructions. Patients in Cohort 1 with non-squamous disease may begin folic acid supplementation at the time of loss of clinical benefit or unacceptable toxicity in Stage 1 in anticipation of pemetrexed-based treatment. Patients should receive anti-emetic and IV hydration for platinum-based treatments according to the local standard of care and manufacturer's instructions.

Pemetrexed and carboplatin will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for pemetrexed and carboplatin dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A14–5.1.5. Pemetrexed and carboplatin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A14–4.2 CONCOMITANT THERAPY FOR ATEZO + PEM + CARBO ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For details regarding the concomitant therapies for pemetrexed and carboplatin, refer to the pemetrexed and carboplatin prescribing information.

A14–4.2.1 Permitted Therapy for Atezo + Pem + Carbo Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards

- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A14–4.2.3).

- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab, pemetrexed, and carboplatin may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive limited-field radiotherapy to the brain (stereotactic radiosurgery) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A14–4.2.2 and A14–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension,

wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A14–4.2.2 Cautionary Therapy for Atezo + Pem + Carbo Arm

A14–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A14–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A14–4.2.3) may be used during the study at the discretion of the investigator.

A14–4.2.2.3 Non-Steroidal Anti-Inflammatory Drugs

Caution should be used when administering ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently with pemetrexed in patients with mild to moderate renal insufficiency (creatinine clearance 45–79 mL/min). Patients eligible for pemetrexed therapy should avoid taking NSAIDs for at least 2 days prior to pemetrexed administration if the NSAID has a short elimination half-life, for at least 5 days prior to pemetrexed administration if the NSAID has a long elimination half-life, on the day of pemetrexed administration, and at least 2 days following pemetrexed administration.

A14–4.2.3 Prohibited Therapy for Atezo + Pem + Carbo Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A14–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Non-steroidal anti-inflammatory drugs with long elimination half-lives are prohibited for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration.

A14–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + PEM + CARBO ARM

Contraception requirements for women and men in the Atezo + Pem + Carbo arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of atezolizumab and 6 months after the last dose of pemetrexed or carboplatin

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of pemetrexed or carboplatin. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of pemetrexed or carboplatin to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A14–5 ASSESSMENT OF SAFETY FOR ATEZO + PEM + CARBO ARM

A14–5.1 SAFETY PLAN FOR ATEZO + PEM + CARBO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and chemotherapy in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A14–5.1.1, A14–5.1.2, A14–5.1.3, and A14–5.1.4). Guidelines for management of patients who experience specific adverse events are provided in Section A14–5.1.5.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A14–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A14–5.1.2 Risks Associated with Pemetrexed

The most common side effects of pemetrexed include gastrointestinal symptoms (nausea, vomiting, diarrhea, or constipation), myelosuppression, infection, fatigue, stomatitis, loss of appetite, and rash.

For more details regarding the safety profile for pemetrexed, refer to the pemetrexed prescribing information.

A14–5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression, including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic.

For more details regarding the safety profile for carboplatin, refer to the carboplatin prescribing information.

A14–5.1.4 Risks Associated with Combination Use of Atezolizumab, Pemetrexed, and Carboplatin

According to the safety data from Study GP28328 to date, the risk of overlapping toxicities between atezolizumab, pemetrexed, and carboplatin is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with these chemotherapeutic agents (e.g., dermatitis and infusion-associated reactions) could be exacerbated by the immunostimulatory activity of atezolizumab.

A14–5.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo + Pem + Carbo Arm

On Day 1 of each cycle, patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL), a platelet count of $\geq 100 \times 10^9$/L (100,000/μL), and a creatinine clearance of ≥ 45 mL/min to receive treatment with pemetrexed and carboplatin. Guidelines for the management of hematologic toxicities, nephrotoxicity, and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table 3.

A14–5.1.5.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times, e.g., for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin but may continue treatment with atezolizumab at the investigator's discretion. After dose reduction, the dose will not be escalated during subsequent administrations.

A14–5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for

patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Pemetrexed and carboplatin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table 3).
If pemetrexed or carboplatin have been withheld for > 63 days because of toxicity, the patient should be discontinued from both chemotherapy agents.

If atezolizumab, pemetrexed, or carboplatin are discontinued, one or both of the other drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A14–4.1.2 for information on dose interruptions for reasons other than toxicity.

A14–5.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 3.

The investigator may use discretion in adhering to the guidelines for pemetrexed and carboplatin described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm

Event	Action to Be Taken
Hematologic toxicity: ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count $< 100 \times 10^9$/L (100,000/μL) at the time of scheduled treatment	
Nadir [a] ANC $\geq 0.5 \times 10^9$/L (500/μL), absence of febrile neutropenia, and nadir platelet count $\geq 50 \times 10^9$/L (50,000/μL)	• Continue atezolizumab. Withhold pemetrexed and carboplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume pemetrexed and carboplatin at current dose. [c] If not, permanently discontinue pemetrexed and carboplatin.
Nadir [a] ANC $< 0.5 \times 10^9$/L (500/μL) and nadir [a] platelet count $\geq 50 \times 10^9$/L (50,000/μL) **or** Febrile neutropenia **or** Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) without bleeding	• Withhold atezolizumab, pemetrexed, and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity: ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count $< 100 \times 10^9$/L (100,000/μL) at the time of scheduled treatment (cont.)	
Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) with bleeding	Any occurrence • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. First occurrence • Withhold pemetrexed and carboplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by two levels. [c] If not, permanently discontinue pemetrexed and carboplatin. Second occurrence • Permanently discontinue pemetrexed and carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Nephrotoxicity	
CrCl ≥ 60 mL/min at time of scheduled treatment	• Continue atezolizumab, pemetrexed, and carboplatin.
CrCl ≥ 45 to < 60 mL/min at time of scheduled treatment	• Continue atezolizumab and pemetrexed. Consider reducing the dose of carboplatin or withholding carboplatin as per clinical judgment.
CrCl ≥ 20 to < 45 mL/min at time of scheduled treatment	• Continue atezolizumab. Withhold pemetrexed. Consider reducing the dose of carboplatin or withholding carboplatin as per clinical judgment. • If event improves to CrCl ≥ 45 mL/min within 63 days, [b] resume pemetrexed at current dose. If not, permanently discontinue pemetrexed.
CrCl < 20 mL/min at time of scheduled treatment	• Withhold atezolizumab and pemetrexed. Permanently discontinue carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event improves to CrCl ≥ 45 mL/min within 63 days, [b] resume pemetrexed at current dose. If not, permanently discontinue pemetrexed.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Mucositis	
Mucositis, Grade 1 or 2	• Continue atezolizumab, pemetrexed, and carboplatin.
Mucositis, Grade 3 or 4	Any occurrence • Continue atezolizumab. First occurrence • Withhold pemetrexed and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed with dose reduced by two levels resume carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin. Second occurrence • Permanently discontinue pemetrexed. Withhold carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume carboplatin with dose reduced by one level. [c] If not, permanently discontinue carboplatin. Third occurrence • Permanently discontinue carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m2 and then from 375 to 250 mg/m2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Diarrhea	
Diarrhea, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue pemetrexed and carboplatin.
Diarrhea, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Neurologic toxicity	
Neurologic toxicity, Grade 1	• Follow guidelines for atezolizumab in Appendix 6. • Continue pemetrexed and carboplatin.
Neurologic toxicity, Grade 2	• Follow guidelines for atezolizumab in Appendix 6. • Withhold pemetrexed and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue carboplatin.
Neurologic toxicity, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold pemetrexed and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by two levels. [c] If not, permanently discontinue carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m2 and then from 375 to 250 mg/m2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue pemetrexed and carboplatin.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold pemetrexed and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 6 • Withhold pemetrexed and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 or better within 63 days, b resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Permanently discontinue pemetrexed. • Withhold carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume carboplatin with dose reduced by one level. [c] If not, permanently discontinue carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Pem + Carbo Arm (cont.)

Event	Action to Be Taken
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, pemetrexed, and carboplatin.
Grade 3	• Continue atezolizumab. Withhold pemetrexed and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.
Grade 4	• Withhold atezolizumab, pemetrexed, and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue pemetrexed and carboplatin.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold atezolizumab, pemetrexed, and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume pemetrexed and carboplatin with dose reduced by one level. [c] If not, permanently discontinue pemetrexed and carboplatin.

Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, pemetrexed and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with pemetrexed and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of pemetrexed may be reduced by 125 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 500 to 375 mg/m^2 and then from 375 to 250 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.5 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 6 to 4.5 mg/mL/min and then from AUC of 4.5 to 3 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both pemetrexed and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

A14–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + PEM + CARBO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Pem + Carbo arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis

- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A14–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + PEM + CARBO ARM

A14–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 6 months after the last dose of pemetrexed or carboplatin. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A14–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of pemetrexed or carboplatin. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to pemetrexed or carboplatin. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A14–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A14–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A14–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + PEM + CARBO ARM

Table 4 Schedule of Activities for Atezo + Pem + Carbo Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) [a]			Treat. Discon.	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2		Every 3 Months (±7 days)
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available				
Vital signs [c]		x	x	x	x	
Weight [d]		x		x	x	
Complete physical examination [e]					x	
Limited physical examination [d, f]		x	x	x		
ECOG Performance Status [d]		x		x	x	
ECG [d, g]		Perform as clinically indicated				
Hematology [h]		x [i]	x	x	x	
Chemistry [j]		x [i]	x	x	x	
TSH, free T3 (or total T3), and free T4 [k]		x [i]			x	
Pregnancy test [l]		x		x	x	
Urinalysis [m]		Perform as clinically indicated				
Serum autoantibody sample [n]		Perform if a patient experiences a suspected immune-mediated adverse event				
PK samples		Refer to Table 5				
ADA samples		Refer to Table 5				
Biomarker samples		Refer to Table 5				
Blood sample for RBR (optional) [o]		x				

Table 4 Schedule of Activities for Atezo + Pem + Carbo Arm (cont.)

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) [a]			Treat. Discon.	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2		Every 3 Months (±7 days)
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)		
Tumor biopsy	See Appendix 2	x [p]				
Tumor biopsy (optional)		x [q]				
Tumor response assessments		x [r, s]				
Concomitant medications [t]		x	x	x	x	
Adverse events [u]		x	x	x	x [u]	x
Atezolizumab administration [v, w]		x		x		
Pemetrexed administration [x]		x		x		
Carboplatin administration [y]		x		x		
Survival follow-up and anti-cancer treatment						x [z]

ADA = anti-drug antibody; Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; AUC = area under the concentration–time curve; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after treatment assignment.

[c] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

Table 4 Schedule of Activities for Atezo + Pem + Carbo Arm (cont.)

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] ECG recordings will be obtained as clinically indicated. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[i] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[j] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[k] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[l] All women of childbearing potential will undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[m] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[n] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[o] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[p] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[q] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Table 4 Schedule of Activities for Atezo + Pem + Carbo Arm (cont.)

[r] Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[s] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[t] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment initiation of study treatment until the treatment discontinuation visit.

[u] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[v] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[w] Atezolizumab treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[x] Pemetrexed will be administered by IV infusion at a dose of 500 mg/m^2 over 10 minutes on Day 1 of each cycle. Pemetrexed treatment will continue until unacceptable toxicity or radiographic disease progression according to RECIST v1.1. Pemetrexed will be administered approximately 30 minutes after completion of the atezolizumab infusion.

Table 4 Schedule of Activities for Atezo + Pem + Carbo Arm (cont.)

[y] Carboplatin will be administered by IV infusion to achieve an initial target AUC of 6 mg/mL/min (Calvert formula dosing) over 30–60 minutes on Day 1 of the first four or six cycles, depending on local clinical practice. However, treatment will be discontinued for patients who experience unacceptable toxicity or radiographic disease progression according to RECIST v1.1. Carboplatin will be administered approximately 30 minutes after completion of the pemetrexed infusion.

[z] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Pem + Carbo Arm

Visit	Time	Sample Type
Day 1 of Cycle 1 (start of combination treatment period)	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	At visit	• Biomarkers (plasma and serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (± 30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Pem + Carbo = atezolizumab plus pemetrexed plus carboplatin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.
Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 15
Study Details Specific to the Atezo + Gem + Carbo Arm

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A15–1 BACKGROUND ON ATEZO + GEM + CARBO ARM

A15–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 ([B7-1] also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A15–1.2 BACKGROUND ON GEMCITABINE AND CARBOPLATIN IN NON–SMALL CELL LUNG CANCER

Standard of care for first-line treatment of squamous NSCLC that does not harbor a driver mutation is a platinum doublet consisting of either cisplatin or carboplatin in combination with gemcitabine. Well-designed clinical trials conducted over the last decade have demonstrated that pemetrexed and bevacizumab are not appropriate agents for the treatment of patients with squamous-cell carcinoma of the lung (Johnson et al. 2004; Scagliotti et al. 2008; Sandler et al. 2009). On the other hand, the

combination of gemcitabine and a platinum analog (either cisplatin or carboplatin) has demonstrated efficacy as first-line treatment for squamous NSCLC and, as a result, is often a reference arm in clinical trials to evaluate new therapeutics (Schiller et al. 2002; Treat et al. 2010).

A15–2 RATIONALE FOR ATEZO + GEM + CARBO ARM

A15–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A15–2.2 RATIONALE FOR COMBINING IMMUNE CHECKPOINT INHIBITORS WITH CHEMOTHERAPY

Tumor-cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable this hypothesis to be tested.

Pembrolizumab, a PD-1 inhibitor, has been approved in combination with pemetrexed and carboplatin for the first-line treatment of metastatic non-squamous NSCLC, irrespective of PD-L1 expression. The objective response rate (ORR) for pembrolizumab in combination with pemetrexed and carboplatin (55%; 33 of 60 patients) was nearly double the ORR for pemetrexed and carboplatin alone (29%; 18 of 63 patients). In addition, 92% of patients treated with pembrolizumab plus chemotherapy had a duration of response of 6 months or more, compared with 81% of patients treated with chemotherapy alone. Median PFS was 13.0 months for patients treated with pembrolizumab plus chemotherapy and 8.9 months for patients treated with chemotherapy alone (Langer et al. 2016). The incidence of Grade 3 or higher treatment-related adverse events was similar between groups.

Nivolumab, a PD-1 inhibitor, in combination with platinum-based doublet therapy (including gemcitabine plus cisplatin) demonstrated an acceptable efficacy and safety profile, consistent with the known toxicities of nivolumab and chemotherapy, in chemotherapy-naive patients with NSCLC who were not selected on the basis of PD-L1 expression (Rizvi et al. 2016).

As of 10 February 2015 (data cutoff) in an ongoing Phase Ib study of first-line treatment of NSCLC (Study GP28328), the ORR was 70.6% (12 of 17) for patients treated with atezolizumab plus pemetrexed and carboplatin, 50.0% (8 of 16) for patients treated with atezolizumab plus nab-paclitaxel and carboplatin, and 37.5% (3 of 8) for patients treated with atezolizumab plus paclitaxel and carboplatin. Atezolizumab in combination with chemotherapy was not associated with additive severe (Grade 3 or higher) toxicities. The adverse events observed for atezolizumab in combination with chemotherapy were consistent with the known risks of each study treatment. Detailed clinical study results for Study GP28328 can be found in the Atezolizumab Investigator's Brochure.

A15–2.3 BENEFIT–RISK ASSESSMENT

The efficacy and safety results for pembrolizumab plus chemotherapy (Langer et al. 2016) and for nivolumab plus chemotherapy (Rizvi et al. 2016) and the preliminary efficacy and safety results for atezolizumab plus chemotherapy (Study GP28328) offer

evidence of an acceptable safety profile and a promising therapeutic potential when combining a PD-1 or PD-L1 inhibitor with chemotherapy as treatment for NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A15–3 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A15–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + GEM + CARBO ARM

A15–4.1 TREATMENT IN ATEZO + GEM + CARBO ARM

A15–4.1.1 Formulation, Packaging, and Handling

A15–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A15–4.1.1.2 Gemcitabine

For information on the formulation, packaging, and handling of gemcitabine, refer to the local prescribing information.

A15–4.1.1.3 Carboplatin

For information on the formulation, packaging, and handling of carboplatin, refer to the local prescribing information.

A15–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus gemcitabine plus carboplatin (Atezo + Gem + Carbo) arm will receive treatment as outlined in Table 1. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator

after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). Gemcitabine and carboplatin will be administered for the first four or six cycles, depending on local clinical practice. However, gemcitabine and carboplatin will be discontinued for patients who experience unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). It is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table 1 Treatment Regimen for Atezo + Gem + Carbo Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Gemcitabine 1000 mg/m^2 IV on Days 1 and 8 of the first four or six cycles • Carboplatin AUC 5 mg/mL/min (Calvert formula dosing) IV on Day 1 of the first four or six cycles

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available. For information on overdosing of gemcitabine or carboplatin, refer to the local prescribing information for each agent.

A15–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with anti-histamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.5. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A15–4.1.2.2 Gemcitabine and Carboplatin Administration

Gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 over 30 minutes on Days 1 and 8 of the first four or six 21-day cycles, depending on local clinical practice. Carboplatin will be administered by IV infusion to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) over 30–60 minutes on Day 1 of the first four or six cycles, depending on local clinical practice. Gemcitabine will be administered approximately 30 minutes after completion of the atezolizumab infusion, and carboplatin will be administered approximately 30 minutes after completion of the gemcitabine infusion.

Patients should receive anti-emetic and IV hydration for platinum-based treatments according to the local standard of care and manufacturer's instructions.

Gemcitabine and carboplatin will be administered according to institutional standards in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for gemcitabine and carboplatin dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A15–5.1.5. Gemcitabine and carboplatin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A15–4.2 CONCOMITANT THERAPY FOR ATEZO + GEM + CARBO ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For details regarding the concomitant therapies for carboplatin and gemcitabine, refer to the carboplatin and gemcitabine prescribing information, respectively.

A15–4.2.1 Permitted Therapy for Atezo + Gem + Carbo Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic anticoagulation therapy (such as low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A15–4.2.3).

- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab, gemcitabine, and carboplatin may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive limited-field radiotherapy to the brain (stereotactic radiosurgery) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A15–4.2.2 and A15–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A15–4.2.2 Cautionary Therapy for Atezo + Gem + Carbo Arm

A15–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A15–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A15–4.2.3) may be used during the study at the discretion of the investigator.

A15–4.2.3 Prohibited Therapy for Atezo + Gem + Carbo Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A15–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A15–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + GEM + CARBO ARM

Contraception requirements for women and men in the Atezo + Gem + Carbo arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 5 months after the last dose of atezolizumab and 6 months after the last dose of gemcitabine or carboplatin

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 6 months after the last dose of gemcitabine or carboplatin. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of gemcitabine or carboplatin to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A15–5 ASSESSMENT OF SAFETY FOR ATEZO + GEM + CARBO ARM

A15–5.1 SAFETY PLAN FOR ATEZO + GEM + CARBO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and gemcitabine or carboplatin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A15–5.1.1, A15–5.1.2, A15–5.1.3, and A15–5.1.4). Guidelines for management of patients who experience specific adverse events are provided in Section A15–5.1.5.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A15–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A15–5.1.2 Risks Associated with Gemcitabine

The most common side effects of gemcitabine are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

For more details regarding the safety profile for gemcitabine, refer to the gemcitabine prescribing information.

A15–5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression, including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic.

For more details regarding the safety profile for carboplatin, refer to the carboplatin prescribing information.

A15–5.1.4 Risks Associated with Combination Use of Atezolizumab, Gemcitabine, and Carboplatin

There are no significant overlapping toxicities associated with combination use of atezolizumab with gemcitabine and carboplatin.

A15–5.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo + Gem + Carbo Arm

On Day 1 of each cycle, patients are required to have an ANC of $\geq 1.5 \times 10^9$/L (1500/μL) and a platelet count of $\geq 100 \times 10^9$/L (100,000/μL) to receive treatment with gemcitabine and carboplatin. On Day 8 of each cycle, patients are required to have an ANC of $\geq 0.5 \times 10^9$/L (500/μL) and a platelet count of $\geq 50 \times 10^9$/L (50,000/μL) to receive treatment with gemcitabine. Guidelines for the management of hematologic toxicities, nephrotoxicity, and other toxicities (including guidelines for dose modification and treatment interruption or discontinuation) are provided in Table 3.

A15–5.1.5.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times, e.g., for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin but may continue treatment with atezolizumab at the investigator's discretion. After dose reduction, the dose will not be escalated during subsequent administrations.

A15–5.1.5.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from

atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Gemcitabine and carboplatin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table 3).
If gemcitabine or carboplatin have been withheld for > 63 days because of toxicity, the patient should be discontinued from both chemotherapy agents.

If atezolizumab, gemcitabine, or carboplatin are discontinued, one or both of the other drugs can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A15–4.1.2 for information on dose interruptions for reasons other than toxicity.

A15–5.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 3.

The investigator may use discretion in adhering to the guidelines for gemcitabine and carboplatin described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm

Event	Action to Be Taken
Hematologic toxicity on Day 1: ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count $< 100 \times 10^9$/L (100,000/μL)	
Nadir [a] ANC $\geq 0.5 \times 10^9$/L (500/μL), absence of febrile neutropenia, and nadir platelet count $\geq 50 \times 10^9$/L (50,000/μL)	• Continue atezolizumab. Withhold gemcitabine and carboplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume gemcitabine and carboplatin at current dose. [c] If not, permanently discontinue gemcitabine and carboplatin.
Nadir [a] ANC $< 0.5 \times 10^9$/L (500/μL) and nadir [a] platelet count $\geq 50 \times 10^9$/L (50,000/μL) **or** Febrile neutropenia **or** Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) without bleeding	• Withhold atezolizumab, gemcitabine, and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity on Day 1: ANC $< 1.5 \times 10^9$/L (1500/μL) and/or platelet count $< 100 \times 10^9$/L (100,000/μL) (cont.)	
Nadir [a] platelet count $< 50 \times 10^9$/L (50,000/μL) with bleeding	Any occurrence • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. First occurrence • Withhold gemcitabine and carboplatin. • If ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL) within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by two levels. [c] If not, permanently discontinue gemcitabine and carboplatin. Second occurrence • Permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Hematologic toxicity on Day 8	
ANC $\geq 1.0 \times 10^9$/L (1000/μL), absence of febrile neutropenia, and platelet count $\geq 100 \times 10^9$/L (100,000/μL)	• Continue gemcitabine at current dose.
ANC 0.5–0.99 $\times 10^9$/L (500–999/μL) **or** Febrile neutropenia **or** Platelet count 50–99 $\times 10^9$/L (50,000–90,000/μL)	• Continue gemcitabine with dose reduced by one level. [c]
ANC $< 0.5 \times 10^9$/L (500/μL) **or** Platelet count $< 50 \times 10^9$/L (50,000/μL)	• Withhold gemcitabine. • Treatment may be resumed on Day 1 of the next cycle if ANC is $\geq 1.5 \times 10^9$/L (1500/μL) and platelet count is $\geq 100 \times 10^9$/L (100,000/μL).

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Nephrotoxicity	
CrCl ≥ 60 mL/min at time of scheduled treatment	• Continue atezolizumab, gemcitabine, and carboplatin.
CrCl ≥ 30 to < 60 mL/min at time of scheduled treatment	• Continue atezolizumab and gemcitabine. Consider reducing the dose of carboplatin or withholding carboplatin as per clinical judgment.
CrCl ≥ 20 to < 30 mL/min at time of scheduled treatment	• Continue atezolizumab. Withhold gemcitabine. Consider reducing the dose of carboplatin or withholding carboplatin as per clinical judgment. • If event improves to CrCl ≥ 30 mL/min within 63 days, [b] resume gemcitabine at current dose. If not, permanently discontinue gemcitabine.
CrCl < 20 mL/min at time of scheduled treatment	• Withhold atezolizumab and gemcitabine. Permanently discontinue carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event improves to CrCl ≥ 30 mL/min within 63 days, [b] resume gemcitabine at current dose or with dose reduced by one level (decision based on best clinical judgment).
Mucositis	
Mucositis, Grade 1 or 2	• Continue atezolizumab, gemcitabine, and carboplatin.
Mucositis, Grade 3 or 4	• Continue atezolizumab. Withhold gemcitabine and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Diarrhea	
Diarrhea, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Diarrhea, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.
Neurologic toxicity	
Neurologic toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Neurologic toxicity, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m2 and then from 750 to 500 mg/m2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Pulmonary toxicity	
Pulmonary toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Pulmonary toxicity, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue gemcitabine. Withhold carboplatin. • If event improves, resume carboplatin at current dose. If not, permanently discontinue carboplatin.
Hepatic toxicity	
Hepatic toxicity, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Hepatic toxicity, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue gemcitabine. Withhold carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume carboplatin with dose reduced by one level. [c] If not, permanently discontinue carboplatin.
Hepatic toxicity, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Hemolytic-uremic syndrome	
Hemolytic-uremic syndrome, any grade	• Permanently discontinue gemcitabine. Withhold atezolizumab and carboplatin. • If event improves, resume atezolizumab and carboplatin at current dose. If not, permanently discontinue atezolizumab and carboplatin.
Capillary leak syndrome	
Capillary leak syndrome, any grade	• Permanently discontinue gemcitabine. Withhold atezolizumab and carboplatin. • If event improves, resume atezolizumab and carboplatin at current dose. If not, permanently discontinue atezolizumab and carboplatin.
Posterior reversible encephalopathy syndrome	
Posterior reversible encephalopathy syndrome, any grade	• Permanently discontinue gemcitabine. Withhold atezolizumab and carboplatin. • If event improves, resume atezolizumab and carboplatin at current dose. If not, permanently discontinue atezolizumab and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 6 • Withhold gemcitabine and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Permanently discontinue gemcitabine. • Withhold carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume carboplatin with dose reduced by one level. [c] If not, permanently discontinue carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m2 and then from 750 to 500 mg/m2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Gem + Carbo Arm (cont.)

Event	Action to Be Taken
Chemotherapy-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab, gemcitabine, and carboplatin.
Grade 3	• Continue atezolizumab. Withhold gemcitabine and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.
Grade 4	• Withhold atezolizumab, gemcitabine, and carboplatin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin with dose reduced by one level. [c] If not, permanently discontinue gemcitabine and carboplatin.
Atezolizumab-related toxicity not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue gemcitabine and carboplatin.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold gemcitabine and carboplatin. • If event resolves to Grade 1 or better within 63 days, [b] resume gemcitabine and carboplatin at current dose or with dose reduced by one level, as determined by the Medical Monitor. [c] If not, permanently discontinue gemcitabine and carboplatin.

Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; AUC = area under the concentration–time curve; CrCl = creatinine clearance.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, gemcitabine and carboplatin can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with gemcitabine and carboplatin should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of gemcitabine may be reduced by 250 mg/m^2 (one dose level) up to two times for management of drug-related toxicities (i.e., from 1000 to 750 mg/m^2 and then from 750 to 500 mg/m^2). The dose of carboplatin may be reduced by AUC of 1.25 mg/mL/min (one dose level) up to two times for management of drug-related toxicities (i.e., from AUC of 5 to 3.75 mg/mL/min and then from AUC of 3.75 to 2.5 mg/mL/min). If further dose reduction is indicated after two dose reductions, the patient must discontinue both gemcitabine and carboplatin. After dose reduction, the dose will not be escalated during subsequent administrations.

A15–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + GEM + CARBO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Gem + Carbo arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A15–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + GEM + CARBO ARM

A15–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 6 months after the last dose of gemcitabine or carboplatin. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A15–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of gemcitabine or carboplatin. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to gemcitabine or carboplatin. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A15–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A15–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A15–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + GEM + CARBO ARM

Table 4 Schedule of Activities for Atezo + Gem + Carbo Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) [a]					Treat. Discon.	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]			Cycles ≥2			
		Day 1	Day 8 (±1 day) [c]	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day) [c]		
Molecular profile of lung cancer (if applicable)	See Appendix 2	Whenever updated information becomes available						
Vital signs [d]		x	x	x	x	x	x	
Weight [e]		x			x		x	
Complete physical examination [f]							x	
Limited physical examination [e, g]		x	x	x	x	x		
ECOG Performance Status [e]		x			x		x	
ECG [e, h]		x			x			
Hematology [i]		x [j]	x	x	x	x	x	
Chemistry [k]		x [j]	x	x	x	x	x	
TSH, free T3 (or total T3), and free T4 [l]		x [j]					x	
C-reactive protein		x	x	x	x	x		
Pregnancy test [m]		x			x		x	
Urinalysis [n]		Perform as clinically indicated						
Serum autoantibody sample [o]		Perform if a patient experiences a suspected immune-mediated adverse event						

Table 4 Schedule of Activities for Atezo + Gem + Carbo Arm (cont.)

Assessment/Procedure	Stage 2 Screening	Treatment Cycles (21-Day Cycles) [a]					Treat. Discon.	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]			Cycles ≥2			
		Day 1	Day 8 (±1 day) [c]	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day) [c]		
PK samples	See Appendix 2	Refer to Table 5						
ADA samples		Refer to Table 5						
Biomarker samples		Refer to Table 5						
Blood sample for RBR (optional) [p]		x						
Tumor biopsy		x [q]						
Tumor biopsy (optional)		x [r]						
Tumor response assessments		x [s, t]						
Concomitant medications [u]		x	x	x	x	x	x	
Adverse events [v]		x	x	x	x	x	x	x
Atezolizumab administration [w, x]		x			x			
Gemcitabine administration [y]		x	x		x	x		
Carboplatin administration [z]		x			x			
Survival follow-up and anti-cancer treatment								x [aa]

ADA = anti-drug antibody; Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table 4 Schedule of Activities for Atezo + Gem + Carbo Arm (cont.)

[c] The Day 8 visit needs to be performed only for the the first 4 or 6 cycles of gemcitabine and carboplatin administration, depending on local clinical practice.

[d] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[e] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[f] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] ECG recordings will be obtained as clinically indicated. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[i] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[j] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[l] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[m] All women of childbearing potential will undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[n] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[o] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[p] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

Table 4 Schedule of Activities for Atezo + Gem + Carbo Arm (cont.)

[q] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[r] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[s] Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[t] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[u] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from initiation of study treatment until the treatment discontinuation visit.

[v] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[w] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

Table 4 Schedule of Activities for Atezo + Gem + Carbo Arm (cont.)

[x] Atezolizumab treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[y] Gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 over 30 minutes on Days 1 and 8 of the first four or six cycles, depending on local clinical practice. However, treatment will be discontinued for patients who experience unacceptable toxicity or disease progression according to RECIST v1.1. Gemcitabine will be administered approximately 30 minutes after completion of the atezolizumab infusion.

[z] Carboplatin will be administered by IV infusion to achieve an initial target area under the concentration–time curve (AUC) of 5 mg/mL/min (Calvert formula dosing) over 30–60 minutes on Day 1 of the first four or six cycles, depending on local clinical practice. However, treatment will be discontinued for patients who experience unacceptable toxicity or disease progression according to RECIST v1.1. Carboplatin will be administered approximately 30 minutes after completion of the gemcitabine infusion.

[aa] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Gem + Carbo Arm

Visit	Time	Sample Type
Day 1 of Cycle 1 (start of combination treatment period)	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	At visit	• Biomarkers (plasma and serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (± 30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Gem + Carbo = atezolizumab plus gemcitabine plus carboplatin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.
Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 16
Study Details Specific to the Atezo + Docetaxel Arm (Stages 1 and 2)

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A16–1 BACKGROUND ON ATEZO + DOCETAXEL ARM

A16–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 ([B7-1] also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A16–1.2 BACKGROUND ON DOCETAXEL

Docetaxel is a commonly used standard treatment option after failure of platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC. It has demonstrated a survival benefit relative to best supportive care in patients with relapsed NSCLC following first-line therapy and is associated with a response rate of 6%–11% and a median overall survival (OS) of 5–10 months (Stinchcombe and Socinski 2008; Ramlau et al. 2012).

A16–2 RATIONALE FOR ATEZO + DOCETAXEL ARM

A16–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A16–2.2 RATIONALE FOR COMBINING IMMUNE CHECKPOINT INHIBITORS WITH CHEMOTHERAPY

Tumor-cell killing by cytotoxic chemotherapy can reasonably be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007). Evaluating the safety and efficacy of these treatment combinations in patients with NSCLC will enable this hypothesis to be tested.

Recently, the combination of pembrolizumab with carboplatin/cisplatin and pemetrexed was approved by the U.S. FDA for patients with non-squamous NSCLC based on the Phase II study KEYNOTE-021. The objective response rate (ORR) for pembrolizumab in combination with pemetrexed and carboplatin (55%; 33 of 60 patients) was nearly double the ORR for pemetrexed and carboplatin alone (29%; 18 of 63 patients). In addition, 92% of patients treated with pembrolizumab plus chemotherapy had a duration of response of 6 months or more compared with 81% of patients treated with chemotherapy alone. Median PFS was 13.0 months for patients treated with pembrolizumab plus chemotherapy and 8.9 months for patients treated with chemotherapy alone (Langer et al. 2016). The incidence of Grade 3 or higher treatment-related adverse events was similar between groups.

These results have been confirmed for patients with non-squamous NSCLC in the Phase III study KEYNOTE-189. The triplet combination demonstrated a significantly longer median OS in the intent-to-treat population than chemotherapy alone (HR = 0.49; $p < 0.0001$). Median PFS was also significantly longer for the experimental arm (8.8 months vs. 4.9 months; HR = 0.52, $p < 0.0001$) (Gandhi et al. 2018). This combination may replace platinum-based chemotherapy regimens as a standard of care for patients who were previously untreated with advanced-stage non-squamous NSCLC with low PD-L1 expression.

In the Phase III study KEYNOTE-407, the combination of pembrolizumab with carboplatin plus either paclitaxel or nanoparticle albumin-bound (nab)-paclitaxel demonstrated a statistically significant OS benefit compared with the control arm of carboplatin plus nab-paclitaxel (HR = 0.64; 95% CI: 0.49, 0.85; $p < 0.001$). The OS benefit was consistent across all levels of PD-L1 expression. The median PFS was 6.4 months (95% CI: 6.2, 8.3) in the pembrolizumab combination group and 4.8 months (95% CI: 4.3, 5.7) in the placebo combination group (HR = 0.56; 95% CI: 0.45, 0.70; $p < 0.001$) (Paz-Ares et al. 2018). On the basis of these results, the FDA has approved the combination of pembrolizumab plus carboplatin plus nab-paclitaxel for the first-line treatment of patients with squamous NSCLC.

As of 10 February 2015 (data cutoff) in an ongoing Phase Ib study of first-line treatment of NSCLC (Study GP28328), the ORR was 70.6% (12 of 17) for patients treated with atezolizumab plus pemetrexed and carboplatin, 50.0% (8 of 16) for patients treated with atezolizumab plus nab-paclitaxel and carboplatin, and 37.5% (3 of 8) for patients treated with atezolizumab plus paclitaxel and carboplatin. Atezolizumab in combination with chemotherapy was not associated with additive severe (Grade 3 or higher) toxicities. The adverse events observed for atezolizumab in combination with chemotherapy were consistent with the known risks of each study treatment.

More recently, in the Phase III IMpower150 study, the combination of atezolizumab and bevacizumab plus carboplatin and paclitaxel demonstrated a significant increase in PFS

compared with bevacizumab plus carboplatin and paclitaxel in patients with metastatic non-squamous NSCLC (ITT population: HR = 0.62; 95% CI: 0.52, 0.74; p < 0.001) . Furthermore, a significant and clinically meaningful improvement in median OS was observed for the atezolizumab-containing group at the second interim analysis (19.2 months vs. 14.7 months; stratified HR = 0.78; 95% CI, 0.64, 0.96; p = 0.02) (Socinski et al. 2018).

Detailed clinical study results for Study GP28328 and IMpower150 can be found in the Atezolizumab Investigator's Brochure

A16–2.3 BENEFIT–RISK ASSESSMENT

The efficacy and safety results for pembrolizumab plus chemotherapy (Langer et al. 2016) and the preliminary efficacy and safety results for atezolizumab plus chemotherapy (Study GP28328), as well as the recent results from the Phase III studies KEYNOTE-189 (Gandhi et al., 2018), KEYNOTE-407 (Paz-Ares et al., 2018), and Impower150 (Soczinski et al., 2018) offer evidence of an acceptable safety profile and a very promising therapeutic potential when combining a PD-1 or PD-L1 inhibitor with chemotherapy as treatment for NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A16–3 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A16–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + DOCETAXEL ARM

A16–4.1 TREATMENT IN ATEZO + DOCETAXEL ARM

A16–4.1.1 Formulation, Packaging, and Handling

A16–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A16–4.1.1.2 Docetaxel

For information on the formulation, packaging, and handling of docetaxel, refer to the local prescribing information.

A16–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus docetaxel (Atezo + Docetaxel) arm will receive treatment as outlined in Table 1. Patients will continue atezolizumab until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details) and will continue docetaxel until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1. For Stage 1, it is recommended that treatment be initiated no later than 7 days after randomization. For Stage 2, it is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table 1 Treatment Regimen for Atezo + Docetaxel Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Docetaxel 75 mg/m^2 IV over 1 hour on Day 1 of each cycle

Atezo + Docetaxel = atezolizumab plus docetaxel.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available. For information on overdosing of docetaxel, refer to the local prescribing information for each agent.

A16–4.1.2.1 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions

• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A16–4.1.2.2 Docetaxel Administration

Docetaxel will be administered by IV infusion at a dose of 75 mg/m^2 over 60 minutes on Days 1 of each 21-day cycle. Docetaxel will be administered approximately 30 minutes after completion of the atezolizumab infusion.

Docetaxel will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. To reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions, patients should be premedicated with corticosteroids according to local practice (e.g., 8 mg of oral dexamethasone administered twice daily) for 3 days, starting 1 day prior to docetaxel administration. Anti-emetic medications may be administered prophylactically according to local practice at the investigator's discretion.

Guidelines for docetaxel dose modification and treatment interruption or discontinuation because of toxicities are provided in Section A16–5.1.4. Docetaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A16–4.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit to atezolizumab as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to docetaxel will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 3, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 3 Stage 2 Treatment Regimens Available for the Atezo + Docetaxel Arm

Study Treatment	Appendix
Atezo + Lina	

Atezo = atezolizumab; Lina = linagliptin.

A16–4.2 CONCOMITANT THERAPY FOR ATEZO + DOCETAXEL ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For details regarding the concomitant therapies for docetaxel, refer to the docetaxel prescribing information.

A16–4.2.1 Permitted Therapy for Atezo + Docetaxel Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin at a stable dose)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19)*

  Live, attenuated vaccines are not permitted (see A16–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and docetaxel may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive limited-field radiotherapy to the brain (stereotactic radiosurgery) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A16–4.2.2 and A16–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A16–4.2.2 Cautionary Therapy for Atezo + Docetaxel Arm

A16–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A16–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A16–4.2.3) may be used during the study at the discretion of the investigator.

A16–4.2.2.3 CYP3A4 Inhibitors and Inducers

The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) and strong CYP3A4 inducers should be avoided.

A16–4.2.3 Prohibited Therapy for Atezo + Docetaxel Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A16–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A16–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + DOCETAXEL ARM

Contraception requirements for women and men in the Atezo + Docetaxel arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of atezolizumab and 6 months after the last dose of docetaxel

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 6 months after the last dose of docetaxel. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of docetaxel to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A16–5 ASSESSMENT OF SAFETY FOR ATEZO + DOCETAXEL ARM

A16–5.1 SAFETY PLAN FOR ATEZO + DOCETAXEL ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and chemotherapy in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A16–5.1.1, A16–5.1.2, and A16–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A16–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A16–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A16–5.1.2 Risks Associated with Docetaxel

The most common side effects of docetaxel include infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

For more details regarding the safety profile for docetaxel, refer to the docetaxel prescribing information.

A16–5.1.3 Risks Associated with Combination Use of Atezolizumab and Docetaxel

There are no significant overlapping toxicities associated with combination use of atezolizumab and docetaxel.

A16–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Docetaxel Arm

A16–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab in this study.

The dose of docetaxel can be reduced to 55 mg/m^2 for management of drug-related toxicities. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

A16–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Appendix 6). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Docetaxel treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment (see Table 4). If docetaxel has been withheld for >63 days because of toxicity, the patient should be discontinued from docetaxel.

If atezolizumab is discontinued, docetaxel can be continued if the patient is likely to derive clinical benefit, as determined by the investigator. If docetaxel is discontinued,

atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A16–4.1.2 for information on dose interruptions for reasons other than toxicity.

A16–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 4.

The investigator may use discretion in adhering to the guidelines for docetaxel described below, taking into account the severity of the event and benefit versus risk for the patient, with the goal of maximizing patient compliance and access to supportive care. Additionally, the prescribing information, as well as local hospital or clinical practice must be followed.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm

Event	Action to Be Taken
Hematologic toxicity	
Nadir [a] ANC $< 0.5 \times 10^9$/L (500/μL) for ≥ 7 days [a] **or** Febrile neutropenia	Any occurrence • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. First occurrence • Withhold docetaxel. • If event resolves to ANC $\geq 1.5 \times 10^9$/L (1500/μL) within 63 days, [b] and platelet count is $\geq 100 \times 10^9$/L (100,000/μL), resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Hepatotoxicity	
ALT/AST > 1.5 × ULN in combination with ALP > 2.5 × ULN	• Follow guidelines for atezolizumab in Appendix 6. • Withhold docetaxel. • If event resolves to baseline within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel.
Bilirubin > 1 × ULN **or** ALT/AST > 3.5 × ULN in combination with ALP > 6 × ULN	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue docetaxel.

Atezo + Docetaxel = atezolizumab plus docetaxel; ULN = upper limit of normal.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Neurologic toxicity	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue docetaxel.
Grade 3	• Follow guidelines for atezolizumab in . First occurrence • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days,[b] resume docetaxel with dose reduced to 55 mg/m^2.[c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue docetaxel.
Hypersensitivity reaction	
Grade 1 or 2	• Continue docetaxel at the discretion of the investigator.
Grade 3 or 4	• Immediate discontinuation of the docetaxel infusion and aggressive therapy. Permanently discontinue docetaxel.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Pleural effusion	
Grade 1	• Continue docetaxel and atezolizumab. • Monitor patient closely for possible exacerbation.
Grade 2	• Continue docetaxel and atezolizumab. • Monitor patient closely (e.g., by ultrasound Q2W). • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). • Consider thoracentesis if clinically indicated. • Consider consultation with thoracic surgeon.
Grade 3	<u>First occurrence</u> • Withhold docetaxel treatment until resolution to Grade ≤ 1. • Continue atezolizumab. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • Consider consultation with thoracic surgeon. • If event resolves to Grade ≤ 1 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Withhold atezolizumab until resolution to Grade ≤ 1. • Consider treatment measures as outlined for first occurrence. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	• Permanently discontinue docetaxel. • Withhold atezolizumab until resolution to Grade ≤ 1. • Consider treatment measures as outlined for Grade 3 events. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Pericardial effusion	
Grade 2	• Continue docetaxel and atezolizumab. • Monitor patient closely for possible exacerbation. • Consider initiation of standard treatment measures. • Consider consultation with cardiologist.
Grade 3	<u>First occurrence</u> • Withhold docetaxel until resolution to Grade ≤2. • Continue atezolizumab. • Monitor patient closely (e.g., by ECG and echocardiography weekly). • Initiate standard treatment measures. • Consider consultation with cardiologist. • If event resolves to Grade ≤2 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Withhold atezolizumab for up to 12 weeks until resolution to Grade ≤2. • Consider treatment measures as outlined for first occurrence. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	• Permanently discontinue docetaxel. • Withhold atezolizumab until resolution to Grade ≤2. • Consider treatment measures as outlined for Grade 3 events. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Ascites	
Grade 1	• Continue docetaxel and atezolizumab. • Monitor patient closely for possible exacerbation.
Grade 2	• Withhold docetaxel until resolution to Grade ≤ 1. • Continue atezolizumab. • Monitor patient closely (e.g., by ultrasound Q2W). • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic). • Consider paracentesis if clinically indicated.
Grade 3	<u>First occurrence:</u> • Withhold docetaxel treatment until resolution to Grade ≤ 1. • Continue atezolizumab. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • Consider paracentesis if clinically indicated If event resolves to Grade ≤ 2 within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Withhold atezolizumab treatment until resolution to Grade ≤ 1. • Consider treatment measures as outlined for first occurrence. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.
Grade 4	• Permanently discontinue docetaxel. • Withhold atezolizumab until resolution to Grade ≤ 1. • Consider treatment measures as outlined for Grade 3 events. • If event resolves within 12 weeks, resume atezolizumab at the previous dose level. If not, permanently discontinue atezolizumab.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Fluid retention (other than pleural effusion, pericardial effusion, or ascites)	
Grade 1	• Continue atezolizumab and docetaxel.
Grade 2	• Continue atezolizumab and docetaxel. • Monitor patient closely. • Consider initiation of standard treatment measures (e.g., salt restriction, oral diuretic).
Grade 3	<u>Any occurrence</u> • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. <u>First occurrence</u> • Withhold docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic). • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. <u>Second occurrence</u> • Permanently discontinue docetaxel. • Initiate standard treatment measures (e.g., salt restriction, oral diuretic).

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to Be Taken
Dermatologic events	
Dermatologic event, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue atezolizumab and docetaxel.
Dermatologic event, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. Any occurrence • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. First occurrence • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days,[b] resume docetaxel with dose reduced to 55 mg/m^2.[c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Dermatologic event, Grade 4	• Follow guidelines for atezolizumab in Appendix 6 • Permanently discontinue docetaxel.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Permanently discontinue docetaxel.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Docetaxel Arm (cont.)

Event	Action to be taken
Docetaxel-related non-hematologic toxicity not described above	
Grade 1 or 2	• Continue atezolizumab and docetaxel.
Grade 3	Any occurrence • Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab. First occurrence • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel with dose reduced to 55 mg/m^2. [c] If not, permanently discontinue docetaxel. Second occurrence • Permanently discontinue docetaxel.
Grade 4	• Permanently discontinue docetaxel. Withhold atezolizumab. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Atezolizumab-related toxicity not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue docetaxel.
Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold docetaxel. • If event resolves to Grade 1 or better within 63 days, [b] resume docetaxel at current dose or with dose reduced by one level. The Medical Monitor is available to advise as needed. If not, permanently discontinue docetaxel.

[a] Nadir of prior cycle.

[b] If the investigator believes the patient is likely to derive clinical benefit, docetaxel can be resumed after being withheld for > 63 days. *The decision to re-challenge patients with docetaxel should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] The dose of docetaxel can be reduced to 55 mg/m^2. If further dose reduction is indicated, the patient must discontinue docetaxel. After dose reduction, the dose of docetaxel will not be escalated to 75 mg/m^2.

A16–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + DOCETAXEL ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Docetaxel arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia

- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A16–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + DOCETAXEL ARM

A16–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab and 6 months after the last dose of docetaxel. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A16–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of docetaxel. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to docetaxel. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the investigator and/or obstetrician.

A16–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A16–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A16–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + DOCETAXEL ARM

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2)

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2		
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months (±7 days)
Molecular profile of lung cancer (if applicable)	See Appendix 2	Whenever updated information becomes available				
Vital signs [e]		x	x	x	x	
Weight [f]		x		x	x	
Complete physical examination [g]					x	
Limited physical examination [f, h]		x	x	x		
ECOG Performance Status [f]		x		x	x	
ECG [f, i]		Perform as clinically indicated				
Hematology [j]		x [k]	x	x	x	
Chemistry [l]		x [k]	x	x	x	
TSH, free T3 (or total T3), and free T4 [m]		x [k]			x	
Pregnancy test [n]		x		x	x	
Blood sample for blood-based NGS ctDNA test					x	
Urinalysis [o]		Perform as clinically indicated				
Serum autoantibody sample [p]		Perform if a patient experiences a suspected immune-mediated adverse event				

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2) (cont.)

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Treatment Cycles (21-Day Cycles) [a]			Stage 2 Screen. (see Appendix 2) [c] or Treat. Discon. [d] (see below)	Follow-Up Every 3 Months (±7 days)
		Cycle 1 [b]		Cycles ≥2		
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)		
PK samples	See Appendix 2	Refer to Table 6				
ADA samples		Refer to Table 6				
Biomarker samples		Refer to Table 6				
Blood sample for RBR (optional) [q]		x				
Tumor biopsy		x [r]				
Tumor biopsy (optional)		x [s]				
Tumor response assessments		x [t, u, v]				
Concomitant medications [w]		x	x	x	x	
Adverse events [x]		x	x	x	x	x
Atezolizumab administration [y, z]		x		x		
Docetaxel administration [aa]		x		x		
Survival follow-up and anti-cancer treatment						x [bb]

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2) (cont.)

ADA = anti-drug antibody; Atezo + Docetaxel = atezolizumab plus docetaxel; CT = computed tomography; ctDNA = circulating tumor DNA; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; NGS = next-generation sequencing; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization (Stage 1) or treatment assignment (Stage 2).

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients receiving atezolizumab plus docetaxel as Stage 2 treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. Patients receiving atezolizumab plus docetaxel as Stage 1 treatment will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 or patients who have discontinued Stage 2 treatment will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2) (cont.)

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained as clinically indicated. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[k] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[n] All women of childbearing potential will have to undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[p] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[q] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[r] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[s] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2) (cont.)

[t] Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[u] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[v] For patients receiving atezolizumab plus docetaxel as Stage 1 treatment who receive a different treatment combination during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[w] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment initiation of study treatment until the treatment discontinuation visit.

[x] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[y] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

Table 5 Schedule of Activities for Atezo + Docetaxel Arm (Stages 1 and 2) (cont.)

[z] Atezolizumab treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[aa] Docetaxel will be administered by IV infusion at a dose of 75 mg/m^2 over 60 minutes on Day 1 of each cycle. Docetaxel treatment will continue until unacceptable toxicity or radiographic disease progression according to RECIST v1.1. Docetaxel will be administered approximately 30 minutes after completion of the atezolizumab infusion.

[bb] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Docetaxel Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (± 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo + Docetaxel = atezolizumab plus docetaxel; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.
Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 17
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A17–1 BACKGROUND ON ATEZO + LINA ARM

A17–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 ([B7-1] also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness endocrinopathies, hepatitis or transaminitis, pneumonitis colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A17–1.2 BACKGROUND ON LINAGLIPTIN

Linagliptin, marketed under the registered names Tradjenta® (United States) and Trajenta® (worldwide), is a dipeptidyl peptidase-4 (DPP-4) inhibitor developed for the treatment of Type 2 diabetes mellitus. Once a day (QD) linagliptin at a dose of 5 mg was approved by the U.S. Food and Drug Administration on 2 May 2011 for the treatment of Type 2 diabetes mellitus. Linagliptin is being marketed by Boehringer Ingelheim and Eli Lilly.

DPP-4 (also known as CD26) is an X-prolyl dipeptidyl peptidase capable of enzymatically removing the first two N-terminal amino acids from a protein. DPP-4 is enzymatically active as both a membrane-bound protein and a soluble protein and is expressed in several tissues and biological fluids in the body. DPP-4 expression and/or activity can be affected by inflammation and malignant transformation (Stecca et al. 1997; Kajiyama et al. 2002).

DPP-4 inhibitors are one of the recently developed therapeutic classes for treatment of hyperglycemia in Type 2 diabetes mellitus. The various agents in the class have differing chemical structures but all act by inhibiting the DPP-4 enzyme, thus prolonging the life of incretin hormones, which in turn raise insulin levels and suppress glucagon secretion in a glucose-dependent manner. As a class, DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin, and to have a good safety profile. In addition, the glucose-dependent mechanism of action is associated with a low rate of hypoglycemic events (Richter et al. 2008).

A17–2 RATIONALE FOR ATEZO + LINA ARM

A17–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including

NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A17–2.2 DPP-4 INHIBITION

In addition to the well-studied ability of DPP-4 to regulate the activity of incretin hormones, DPP-4 has also been shown to regulate the activity of several pro-inflammatory chemokines such as CXCL9, CXCL10, and CXCL11 (Kim et al. 2014). The two chemokines, CXCL9 and CXCL10, and their CXCR3 receptor mediate the recruitment of CXCR3-positive T cells and natural killer (NK) cells into solid cancers (Yang et al. 2006; Gorbachev et al. 2007; Wendel et al. 2008). It has been shown that proteolysis of these chemokines inhibits lymphocyte trafficking, resulting in reduced migration of T cells and NK cells into inflammatory sites such as tumor parenchyma.

Preclinical experiments have shown that DPP-4 inhibition restores CXCL10 activity and promotes immune cell recruitment in the tumor parenchyma, leading to increased tumor control (Barreira da Silva et al. 2015).

A17–2.3 BENEFIT–RISK ASSESSMENT

One potential mechanism to increase responses to a checkpoint-inhibitor is to recruit immune cells to the tumor sites so that an anti–PD-L1 agent can be effective in removing immune inhibitory signals in the tumor microenvironment.

Inhibition of DPP-4 activity is one strategy to promote lymphocyte recruitment in tumors, acting by re-establishing functional chemokine gradients. This strategy has achieved proof of concept in preclinical models in which DPP-4 inhibition improved the anti-tumorigenic activity of anti–PD-L1 (Barreira da Silva et al. 2015). Specifically, it was demonstrated that DPP-4 inhibitors, used in combination with checkpoint inhibitors, resulted in 100% protection of tumor-bearing mice (harboring CT-26 colon carcinoma), rejecting their tumor by Day 21, whereas checkpoint inhibition alone protected only 42% of the mice during the same period of time. DPP-4 inhibition, by regulating lymphocytes trafficking, is therefore postulated to enhance the response to current tumor immunotherapy regimens.

Taking into account the potentially synergistic mechanisms of action of atezolizumab and linagliptin, as well as the well known, manageable, and well-tolerated safety profile

for each of these agents, combination treatment with these two agents appears to have a promising and positive benefit–risk in solid tumors such as NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A17–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + LINAGLIPTIN ARM

A17–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The maximum tolerated dose (MTD) of atezolizumab was not reached, and no dose-limiting toxicities (DLTs) were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A17–3.2 RATIONALE FOR LINAGLIPTIN DOSE AND SCHEDULE

The dose of 5 mg once daily (QD), the current approved regimen for patients with Type 2 diabetes (Tradjenta® U.S. Package Insert), was selected on the basis of PK and pharmacodynamic modeling and preclinical results. Linagliptin was tested at single or multiple oral doses of
1–10 mg in healthy volunteers (Graefe-Mody et al. 2012). At steady state, ≥ 80% inhibition of plasma DPP-4 activity was achieved with 5-mg and 10-mg QD dosing. The 10-mg QD dosage led only to a modest increase in inhibition of DPP-4 compared with the 5-mg dosage.

Evidence correlating 80% DPP-4 inhibition in the plasma with increased immune cell infiltration into tumors comes from preclinical experiments performed in mice (unpublished data), and direct evidence of tissue penetration of the drug comes from rats intravenously dosed with linagliptin (Fuchs et al. 2009). Evidence of effective tissue penetration has also been observed in mice receiving a single dose of linagliptin by oral gavage (unpublished data).

A17–3.3 RATIONALE FOR DPP-4 ACTIVITY AS A BIOMARKER

Preclinical experiments with increasing doses of linagliptin in tumor-bearing mice have shown a positive correlation between the percentage of DPP-4 inhibition in plasma and

intra-tumoral lymphocyte infiltration, with 80% plasma inhibition being required to modulate lymphocyte trafficking (unpublished data). To confirm that this inhibition target is indeed achieved, DPP-4 inhibition will be monitored retrospectively in plasma using an enzymatic activity assay (Matheeussen et al. 2012).

Plasma samples will also be used for testing other exploratory biomarkers, including, but not limited to, NH_2-truncated forms of CXCL10 (Decalf et al. 2016). Pretreatment tumor samples will be also tested retrospectively by IHC to identify biomarkers that are predictive of clinical benefit with atezolizumab and + linagliptin combination treatment.

A17–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + LINA ARM

A17–4.1 TREATMENT IN ATEZO + LINA ARM

A17–4.1.1 Formulation, Packaging, and Handling

A17–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A17–4.1.1.2 Linagliptin

For information on the formulation, packaging and handling of linagliptin, refer to the local label.

A17–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus linagliptin (Atezo + Lina) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after treatment assignment.

Table 1 Treatment Regimen for Atezo + Lina Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg IV on Day 1 of each cycle • Linagliptin 5 mg by mouth once daily

Atezo = atezolizumab; IV = intravenous; Lina = linagliptin.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab are available.

A17–4.1.2.1 Linagliptin Administration

Patients will take linagliptin orally QD, one tablet (5 mg) QD of each 21-day cycle. This is the current dosage approved for linagliptin for the treatment of Type 2 diabetes.

On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel. Linagliptin can be taken with or without food. Missed or vomited doses will not be made up.

To assess patient compliance with self-administration of linagliptin, patients will be required to record the time and date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

No dose modification for linagliptin is allowed. Guidelines for linagliptin treatment interruption or discontinuation because of toxicities are provided in Section A17–5.1.4 and the local prescribing information.

Linagliptin treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A17–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion every 15 (±5) minutes during the infusion and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of IRRs are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section A18–5.1.4.2. Atezolizumab treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruptions *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A17–4.2 CONCOMITANT THERAPY FOR ATEZO+LINA ARM

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A17–4.2.1 Permitted Therapy for Atezo + Lina Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Prophylactic antibiotic or anti-viral treatment administered according to institutional standards
- Inactivated *vaccines (such as* influenza *and COVID-19 vaccines)*

  Live, attenuated vaccines are not permitted (see A17–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids and mineralocorticoids (e.g., fludrocortisone) administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab and linagliptin may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of central nervous system (CNS)-directed therapy.
  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
  – Anticonvulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A17–4.2.2 and A17–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence on potential interactions of COVID-19 vaccines with linagliptin. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A17–4.2.2 Cautionary Therapy for Atezo + Lina Arm

A17–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

A17–4.2.2.2 Medications Given with Precaution due to Effects Related to P-Glycoprotein and Cytochrome P450 3A4

Concomitant use of strong inducers of P-glycoprotein and cytochrome P450 3A4 (e.g., rifampicin) should be avoided during linagliptin treatment because exposure will be

decreased in presence of these agents and reduce linagliptin activity. Therefore, use of alternative treatments is strongly recommended during linagliptin treatment.

A17–4.2.2.3 Medications Known to Cause Hypoglycemia

Concomitant use of insulin or insulin-secretagogue drugs are allowed but should be used with caution owing to an increased risk of hypoglycemia. An initial dose decrease in the insulin or insulin-secretagogue drugs should be considered to prevent hypoglycemic events.

A17–4.2.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A17–4.2.3) may be used during the study at the discretion of the investigator.

A17–4.2.3 Prohibited Therapy for Atezo + Lina Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A17–4.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin [IL]-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A17–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + LINA ARM

Contraception requirements for women and men in the Atezo + Linagliptin arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive

method with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of study treatment

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A17–5 ASSESSMENT OF SAFETY FOR ATEZO + LINA ARM

A17–5.1 SAFETY PLAN FOR ATEZO + LINA ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and linagliptin in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A17–5.1.1, A17–5.1.2, and A17–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A17–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. Adverse events will be reported as described in Sections 5.2–5.6.

A17–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6

of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A17–5.1.2 Risks Associated with Linagliptin

Linagliptin is known to cause acute pancreatitis, hypoglycemia, hypersensitivity, arthralgia, bullous pemphigoid, nasopharyngitis, and cough in patients with Type 2 diabetes mellitus. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycemia was increased over that of placebo. Linagliptin alone showed a comparable incidence of hypoglycemia to placebo.

For more details regarding the safety profile of linagliptin, refer to the local prescribing information.

A17–5.1.3 Risks Associated with Combination Use of Atezolizumab + Linagliptin

The following adverse event is a potential overlapping toxicity associated with combination use of atezolizumab and linagliptin: acute pancreatitis, hypersensitivity, cough, arthralgia, rash, and bullous pemphigoid.

A17–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Lina Arm

A17–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or linagliptin in this study.

A17–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 3). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day of oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Linagliptin treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If linagliptin has been withheld for ≥ 21 days

because of toxicity, the patient should be discontinued from linagliptin, unless resumption of treatment is approved *at the investigator's discretion . The decision to re-challenge patients should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

If atezolizumab is discontinued, linagliptin should also be discontinued. If linagliptin is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A17–4.1.2 for information on dose interruptions for reasons other than toxicity.

A17–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events related to linagliptin are provided in the linagliptin prescribing information.

General guidelines for management of patients who experience adverse events in this arm are provided in Table 3. In addition, atezolizumab management guidelines for specific atezolizumab-related adverse events can also be found in Appendix 6.
For cases in which management guidelines are not covered in Appendix 6, the linagliptin prescribing information, or the protocol, patients should be managed as deemed appropriate by the investigator according to best medical judgment.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Pancreatic events	
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab and linagliptin. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., ≥ 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab and linagliptin for up to 12 weeks after event onset. • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events, permanently discontinue atezolizumab and linagliptin and contact the Medical Monitor. [c] • If event resolves to Grade 1 or better within 21 days, resume linagliptin at the current dose. If not, determine whether linagliptin should continue to be withheld or should be permanently discontinued. *The Medical Monitor is available to advise as needed.*

Atezo = atezolizumab; Lina = linagliptin.

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* rechallenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Pancreatic events (cont.)	
Pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a, b] • Permanently discontinue atezolizumab and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Permanently discontinue linagliptin. • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Atezo = atezolizumab; Lina = linagliptin.

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* rechallenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Linagliptin-related toxicities not described above	
Grade 1 or 2	• Continue linagliptin and atezolizumab.
Grade 3	• Withhold linagliptin treatment. Continue atezolizumab. • If event resolves to Grade 2 within 21 days, resume linagliptin. If not, permanently discontinue linagliptin. • If event resolves to Grade 1 or better within 21 days, resume linagliptin. If not, permanently discontinue linagliptin.
Grade 4	• Withhold linagliptin and atezolizumab. • If event resolves to Grade 2 or better within 21 days, resume linagliptin. If not, permanently discontinue linagliptin. • If event improves, resume atezolizumab. If not, permanently discontinue atezolizumab.
Any grade of bullous pemphigoid	• Permanently discontinue linagliptin. • Refer patient to dermatologist. • Initiate treatment as per institutional guidelines. • For Grade 3 event, withhold atezolizumab for up to 12 weeks after event onset, initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For Grade 4 event, permanently discontinue atezolizumab and contact Medical Monitor.

Atezo = atezolizumab; Lina = linagliptin.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* rechallenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Continue linagliptin.
Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Continue linagliptin.
Grade 4	• Follow guidelines for atezolizumab in Appendix 6 • If atezolizumab is discontinued, linagliptin should also be discontinued.

Atezo = atezolizumab; Lina = linagliptin.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* rechallenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A17–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + LINAGLIPTIN ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Linagliptin arm include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an

infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Grade ≥ 3 hypoglycemia
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

A17–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + LINAGLIPTIN ARM

A17–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring

of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A17–5.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A17–5.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A17–6 SCHEDULE OF ACTIVITIES FOR ATEZO + LINA ARM

Table 4 Schedule of Activities for Atezo + Lina Arm

Assessment/Procedure	Stage 2 Screening	Treatment Cycle (21-Day Cycles) [a]			Treatment Discon.	Follow-Up
		Cycle 1 [b]		Cycles ≥2		Every 3 Months (±7 days)
		Day 1	Day 15 (±3 days)	Day 1 (±3 days)		
Molecular profile of lung cancer (if applicable)	See Appendix 2	Whenever updated information becomes available				
Vital signs [c]		x		x	x	
Weight [d]		x		x	x	
Complete physical examination [e]					x	
Limited physical examination [d, f]		x	x	x		
ECOG Performance Status [d]		x		x	x	
ECG [d, g]		Perform as clinically indicated				
Hematology [h]		x [i]	x	x	x	
Chemistry [j]		x [i]	x	x	x	
TSH, free T3 (or total T3), and free T4 [k]		x [i]			x	
C-reactive protein					x	
Pregnancy test [l]		x		x	x	
Urinalysis [m]		Perform as clinically indicated			x	
Serum autoantibody sample [n]		Perform if a patient experiences a suspected immune-mediated adverse event				

Table 4 Schedule of Activities for Atezo + Lina Arm (cont.)

Assessment/Procedure	Stage 2 Screening	Treatment Cycle (21-Day Cycles) [a]			Treatment Discon.	Follow-Up
		Cycle 1 [b]		Cycles ≥ 2		Every 3 Months (± 7 days)
		Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)		
PK samples	See Appendix 2	Refer to Table 5				
ADA samples		Refer to Table 5				
Biomarker samples		Refer to Table 5				
Blood sample for RBR (optional) [o]		x				
Tumor biopsy		x [p]				
Tumor biopsy (optional)		x [q]				
Tumor response assessments		x [r, s]				
Concomitant medications [t]		x	x	x	x	
Adverse events [u]		x	x	x	x	
Atezolizumab administration [v, w]		x		x		
Dispense linagliptin [w, x]		x		x		
Study drug accountability				x [y]		
Survival follow-up and anti-cancer treatment						x [z]

ADA = anti-drug antibody; Atezo + Lina = atezolizumab plus linagliptin; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; PK = pharmacokinetic; QD = once a day; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Table 4 Schedule of Activities for Atezo + Lina Arm (cont.)

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after treatment assignment.

[c] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[d] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[e] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] ECG recordings will be obtained as clinically indicated. It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[i] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[j] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[k] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

Table 4 Schedule of Activities for Atezo + Lina Arm (cont.)

[l] All women of childbearing potential will undergo urine or serum pregnancy tests at specified visits and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[m] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[n] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[o] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[p] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.8 for tissue sample requirements.

[q] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[r] Tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start a new non–protocol-specified anti-cancer therapy.

[s] All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (i.e., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[t] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment initiation of study treatment until the treatment discontinuation visit.

Table 4 Schedule of Activities for Atezo + Lina Arm (cont.)

[u] After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[v] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[w] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[x] Patients will take one 5-mg tablet of linagliptin orally QD during each 21-day cycle. On clinic visit days, patients should take their tablets in the clinic prior to the atezolizumab infusion, as directed by site personnel.

[y] Medication diaries should be collected and reviewed, and unused medications should be collected for assessment of compliance.

[z] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Lina Arm

Visit	Time	Sample Type(s)
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and PBMC)
	30 minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	2 hours postdose oral linagliptin	• Biomarkers (plasma and serum) • Linagliptin PK (plasma)
Day 15 of Cycle 1	Prior to study treatment [a]	• Linagliptin PK (plasma)
Day 1 of Cycle 2	Prior to study treatment [a]	• Atezolizumab PK (serum) • Linagliptin PK (plasma) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, and PBMC)
Day 1 of Cycle 3	Prior to study treatment [a]	• Atezolizumab PK (serum) • Linagliptin PK (plasma) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma and serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; atezo + lina = atezolizumab plus linagliptin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] On Day 15 of Cycle 1 and Day 1 of Cycle 2 and Cycle 3, patients should take their linagliptin tablet in the clinic after the PK and biomarker samples (if applicable) have been obtained.

Table 5 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Lina Arm: Preliminary and Expansion Phases (cont.)

Visit	Time	Sample Type(s)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA = anti-drug antibody; atezo + lina = atezolizumab plus linagliptin; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

[a] On Day 15 of Cycle 1 and Day 1 of Cycle 2 and Cycle 3, patients should take their linagliptin tablet in the clinic after the PK and biomarker samples (if applicable) have been obtained.

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Appendix 18
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A18–1 BACKGROUND ON ATEZO + BEV ARM

A18–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 ([B7-1] also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A18–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every three weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival ([OS] primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (HR = 0.80; 95% CI: 0.69, 0.93; p = 0.003; KM-estimated median: 12.3 months vs. 10.3 months). The OS benefit was supported by the results of progression-free survival ([PFS] HR = 0.65; 95% CI: 0.56, 0.76; KM-estimated median: 6.4 months vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (Bevacizumab 7.5 mg/kg Arm: HR = 0.75; 95% CI: 0.62, 0.91; p = 0.0026; KM-estimated median PFS: 6.7 months vs. 8.1 months)(Bevacizumab 15 mg/kg Arm: HR = 0.82; 95% CI 0.68, 0.98; p = 0.0301; KM-estimated median PFS: 6.5 months vs. 6.1 months). ORR was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical trials.

A18–2 RATIONALE FOR ATEZO + BEV ARM

A18–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation

(Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune checkpoint inhibitors, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A18–2.2 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell (DC) function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In addition, VEGF recruits macrophages into the tumor microenvironment that have a M2 polarization state, which is typically involved in wound-healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte–associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A18–2.3 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For example, VEGF-A inhibits the maturation of DCs (Gabrilovich et al. 1996), promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T-cells that express VEGF-R2 (Voron et al. 2015), and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector $CD8^+$ T cells, but not regulatory T cells (Motz et al. 2014). Anti-VEGF agents such as bevacizumab are well known to promote the normalization of tumor vasculature and thereby increase access of therapeutic agents (Jain 2001). Furthermore, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). In addition, anti-VEGF therapies can reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors (Roland et al. 2009; Voron et al. 2015). The immunomodulatory effect of bevacizumab is expected to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

There is precedence for a beneficial effect of anti-angiogenesis in the context of immunotherapy. In a murine melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). High pretreatment serum VEGF was associated with poor survival following ipilimumab (anti-CTLA-4) monotherapy (Yuan et al. 2014), and synergistic effects were observed in a clinical study combining ipilimumab and bevacizumab, as shown by increased T-cell frequency in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi et al. 2014).

Furthermore, the anti-tumor activity of atezolizumab was increased in combination with bevacizumab, which was associated with a further increase in intra-tumoral CD8+ T cells and increases in gene expression correlated with T-cell trafficking and tumor MHC-I expression and enhanced antigen-specific T-cell migration in metastatic renal cell carcinoma (Wallin et al. 2016).

The above-described data suggest that combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

A18–2.4 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with renal cell carcinoma, mCRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with hepatocellular carcinoma. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced renal cell carcinoma.

In chemotherapy-naive patients with Stage IV NSCLC, results from Phase III Study GO29436 (IMpower150) have shown that atezolizumab in combination with carboplatin+paclitaxel and bevacizumab results in significantly longer OS compared to carboplatin+paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naive patients (Motzer et al. 2018). Phase Ib Study GO30140 in HCC front line found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline alpha feta protein levels, and extraheptic spread. The combination is currently being explored in a randomized Phase III study YO40245 (IMbrave150) versus sorafenib in first-line treatment for HCC (Stein et al. 2018). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A18–2.5 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the checkpoint inhibitor (CPI)-pretreated patient population. Because of the

potentially synergistic mechanisms of action of atezolizumab and bevacizumab, as well as their manageable and tolerable safety profiles (see Section A18–5), combination treatment with these two agents appears to have promising therapeutic potential in solid tumors and may augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A18–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV ARM

A18–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no DLTs were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A18–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle) in combination with atezolizumab. This dose and schedule was selected on the basis of both nonclinical studies and available clinical data and are the doses recommended for use for indications in which bevacizumab is approved. Furthermore, these doses have been previously tested in combination with atezolizumab demonstrating tolerability without exacerbation of bevacizumab or atezolizumab-associated adverse events (refer to the Bevacizumab and Atezolizumab Investigator Brochure for further details).

A18–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + BEV ARM

A18–4.1 TREATMENT IN ATEZO + BEVACIZUMAB

A18–4.1.1 Formulation, Packaging, and Handling

A18–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A18–4.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

For information on the formulation, and handling of bevacizumab, refer to the pharmacy manual and the Bevacizumab Investigator's Brochure

A18–4.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus bevacizumab (Atezo + Bev) arm will receive treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is recommended that treatment be initiated no later than 7 days after randomization.

Table 1 Treatment Regimen for Atezo + Bev Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev = atezolizumab plus bevacizumab.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or bevacizumab are available.

A18–4.1.2.1 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Bevacizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the bevacizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be measured at the end of infusion and 2 (±1) hours after the infusion. • Patients should be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an infusion-related reaction, or 90 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. • Vital signs should be measured within 30 minutes after completion of the infusion.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A18–5.1.4. Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A18–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A18–5.1.4. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A18–4.1.3 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to bevacizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 4, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible.

Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 4 Stage 2 Treatment Regimens Available for the Atezo + Bev Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo = atezolizumab; Bev = bevacizumab; Lina = linagliptin.

Refer to Appendix 16 and Appendix 17 for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A18–4.2 CONCOMITANT THERAPY FOR ATEZO + BEV ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A18–4.2.1 Permitted Therapy for Atezo + Bev Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated *vaccines (such as* influenza *and COVID-19)*

  Live, attenuated vaccines are not permitted (see A18–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.

  – Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab infusions only, at the discretion of the investigator.

Anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to the first doses of study treatment. However, at the discretion of the investigator, anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of study treatment.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A18–4.2.2 and A18–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence to suggest an interaction between the COVID-19 vaccines and bevacizumab. Based on the mechanism of action of bevacizumab, an interaction with the COVID-19 vaccines is unlikely. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

A18–4.2.2 Cautionary Therapy for Atezo + Bev Arm

A18–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

The above list of cautionary medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor *is available to advise as needed* if questions arise regarding medications not listed above.

A18–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A18–4.2.3) may be used during the study at the discretion of the investigator.

A18–4.2.3 Prohibited Therapy for Atezo + Bev Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A18–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day) or equivalent is prohibited.

A18–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV ARM

Contraception requirements for women and men in the Atezo + Bev arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the last dose of atezolizumab and 6 months after the last dose of bevacizumab

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A18–5 ASSESSMENT OF SAFETY FOR ATEZO + BEV ARM

A18–5.1 SAFETY PLAN FOR ATEZO + BEV ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A18–5.1.1, A18–5.1.2, and A18–5.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A18–5.1.4.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Adverse events will be reported as described in Sections 5.2–5.6.

A18–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6

of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A18–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

A18–5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

On the basis of the frequency of adverse events associated with either atezolizumab or bevacizumab, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and bevacizumab: cardiovascular, gastrointestinal, renal, and pulmonary toxicity.

A18–5.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm

A18–5.1.4.1 Dose Modifications

There will be no dose modifications for atezolizumab or bevacizumab in this study.

A18–5.1.4.2 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 5). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with bevacizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

If either study drug is discontinued, the other study drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A18–4.1.2 for information on dose interruptions for reasons other than toxicity.

A18–5.1.4.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 5. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.*

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reaction	
General guidance	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6 • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
IRR to bevacizumab, Grade 1	• Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 2	• Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3–4	• Stop infusion. • Discontinue bevacizumab.

CRS = cytokine-release syndrome; IRR = infusion-related reaction.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
General guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. • Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: <u>Medication</u> – Initiate loperamide (4 mg) every 6 hours around the clock, alternating with diphenoxylate hydrochloride (5 mg)/atropine sulfate (0.5 mg) every 6 hours around the clock, until no loose stools for 24 hours. – If Grade ≥ 2 diarrhea persists after 48 hours of treatment with loperamide and diphenoxylate/atropine, consider initiating second-line agents (e.g., octreotide, budesonide, tincture of opium). <u>Oral Supplementation</u> – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥ 1 diarrhea or vomiting. <u>Dietary Modifications</u> – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade).

CRP = C-reactive protein; GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. c Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 2	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. a, b, c

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month
Gastrointestinal perforation, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Initiate treatment per institutional guidelines.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Bowel obstruction, Grade 2	• Hold bevacizumab for partial obstruction requiring medical intervention. Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Bevacizumab may be restarted upon complete resolution of event.
Bowel obstruction, Grade 3–4	• Hold bevacizumab for complete obstruction. Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at investigator's discretion.
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and bevacizumab. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. Acneiform rash: • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Withhold bevacizumab. • If event resolves to Grade 1 or better, resume bevacizumab. • Permanently discontinue bevacizumab if withheld for >42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 1	• Continue atezolizumab and bevacizumab. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.* • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 2	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to be taken
Pulmonary events (cont.)	
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Bevacizumab may continue at the discretion of the investigator per medical judgment. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with *corticosteroids equivalent to* 1−2 mg/kg/day*IV methylprednisolone*. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Continue bevacizumab.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Continue bevacizumab.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to be taken
Endocrine disorders (cont.)	
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: • Follow guidelines for atezolizumab in Appendix 6 • Continue bevacizumab. TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 6 • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines for atezolizumab in Appendix 6 • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperglycemia, any grade	• Follow guidelines for atezolizumab in Appendix 6 • Continue bevacizumab.
Hypophysitis (pan-hypopituitarism), Grade 2, 3 ,or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment
Amylase and/or lipase elevation, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to be taken
Endocrine disorders (cont.)	
Pancreatitis, Grade 2, 3 , or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Neurologic disorder	
Neuropathy, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab.
Immune-related meningoencephalitis, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to be taken
Ocular toxicity	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	• Continue atezolizumab and bevacizumab. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	• Withhold atezolizumab. Continue bevacizumab. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Bevacizumab may continue at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	• Grade 2 or above, start antihypertensive therapy.
Hypertension Grade 2	• Hold bevacizumab. [a] Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b] • Once blood pressure < 140/90 mmHg, patient may continue bevacizumab therapy.
Hypertension Grade 3	• If blood pressure is not controlled to 140/90 mmHg with medication, discontinue bevacizumab • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]
Hypertension Grade 4	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
Hemorrhage, Grade 1 (excluding cerebral hemorrhage)	<u>All patients:</u> • Continue atezolizumab. <u>Patients not receiving full-dose anticoagulation:</u> • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] <u>Patients receiving full-dose anticoagulation:</u> • Permanently discontinue bevacizumab. [a]

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Hemorrhage, Grade 2 (excluding cerebral hemorrhage)	All patients: • Continue atezolizumab. Patients not receiving full-dose anticoagulation: • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] Patients receiving full-dose anticoagulation: • Permanently discontinue bevacizumab. [a]
Grade 3 hemorrhage (excluding cerebral hemorrhage)	• Discontinue bevacizumab. • Continue atezolizumab.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Discontinue bevacizumab and atezolizumab. [a]

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Venous thromboembolic events	
Venous thromboembolic event Grade ≥ 3	• For Grade 3 thromboembolic events, hold bevacizumab for > 3 weeks. Bevacizumab treatment may be resumed during the period of therapeutic-dose anticoagulant therapy once the level of anticoagulation therapy is stabilized: • Anticoagulant treatment should be administered per institutional guidelines. • After administration of bevacizumab is restarted, if the patient experiences another Grade ≥ 3 venous thromboembolic event, bevacizumab should be discontinued. • For Grade 4 thromboembolic events, discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Arterial thromboembolic events	
Arterial thromboembolic event, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria first occurrence, no diagnosis of nephrotic syndrome	• No bevacizumab dose interruptions for proteinuria < 2+ by dipstick. • For proteinuria 2+ or 3+ by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤ 2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤ 1 g/24 hours. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Proteinuria (cont.)	
Proteinuria second and subsequent occurrences, no diagnosis of nephrotic syndrome	• No bevacizumab dose interruptions for proteinuria < 3+ by dipstick. • For proteinuria 3+ by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤ 2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤ 1 g/24 hr. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Proteinuria with diagnosis of nephrotic syndrome	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Fistula	
Tracheoesophageal fistula, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Fistula (non-tracheoesophageal), Grade 4	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev Arm (cont.)

Event	Action to Be Taken
Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Interrupt dosing of attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. • If bevacizumab is the attributable study drug and the event resolves to Grade ≤ 1 within 42 days, then resume bevacizumab at fixed dose. If not, permanently discontinue bevacizumab. • If atezolizumab is the attributable study drug and the event resolves to Grade ≤ 1 within 12 weeks, then resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

MRI = magnetic resonance imaging; PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A18–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Bev arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscesses, or GI fistulae
- Grade ≥ 2 non-GI fistula or abscess
- Grade ≥ 3 wound-healing complication
- Any grade CNS bleeding
- Grade ≥ 2 hemoptysis
- Other grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥ 3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES)
- Grade ≥ 3 congestive heart failure

A18–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + BEV ARM

A18–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab or 6 months after the last dose of bevacizumab. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A18–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number

or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A18–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A18–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A18–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + BEV ARM

Table 6 Schedule of Activities for Atezo + Bev Arm

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) [a]		Stage 2 Screen. (see Appendix 2) [c] or Treatment Discontinuation [d] (see below)	Follow-Up [d]
		Cycle 1 [b]	Cycles ≥ 2		Every 3 Months (± 7 days)
	Days –28 to –1	Day 1	Day 1 (± 3 days)		
Molecular profile of lung cancer (if available)	See Appendix 2	Whenever updated information becomes available			
Vital signs [e]		x	x	x	
Weight [f]		x	x	x	
Complete physical examination [g]				x	
Limited physical examination [f, h]		x	x		
ECOG Performance Status [f]		x	x	x	
ECG [f, i]		Perform as clinically indicated			
Hematology [j]		x [k, l]	x [k]	x	
Chemistry [m]		x [k, l]	x [k]	x	
Coagulation (INR and aPTT)		x [k]			
TSH, free T3 (or total T3), and free T4 [n]		x [l]		x	
Pregnancy test [o]		x	x	x	
Urinalysis [p]		x	x [q]	x	
Blood sample for blood-based NGS ctDNA test				x	
Serum autoantibody sample [r]		Perform if a patient experiences a suspected immune-mediated adverse event			

Table 6 Schedule of Activities for Atezo + Bev Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Treatment Cycles (21-Day Cycles) [a]		Stage 2 Screen. (see Appendix 2) [c] or Treatment Discontinuation [d] (see below)	Follow-Up [d]
		Cycle 1 [b]	Cycles ≥ 2		Every 3 Months (± 7 days)
	Days –28 to –1	Day 1	Day 1 (± 3 days)		
PK samples	See Appendix 2	Refer to Table 7			
ADA samples		Refer to Table 7			
Biomarker samples		Refer to Table 7			
Blood sample for RBR (optional) [s]		x			
Tumor biopsy		x [t, u]			
Tumor biopsy (optional)		x [t, u]			
Tumor response assessments		x [w, x, y]			
Concomitant medications [z]		x	x	x	
Adverse events [aa]		x	x	x [aa]	x [aa]
Atezolizumab administration [bb, cc]		x	x		
Bevacizumab administration [cc, dd]		x	x		
Survival follow-up and anti-cancer treatment					x [ee]

ADA = anti-drug antibody; Atezo + Bev = atezolizumab plus bevacizumab; CT = computed tomography; ctDNA = circulating tumor DNA; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; MUGA = multiple-gated acquisition; NGS = next-generation sequencing; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen. = screening; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Table 6 Schedule of Activities for Atezo + Bev Arm (cont.)

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after randomization.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent atezolizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion. For the first infusion of bevacizumab, vital signs should be measured within 60 minutes prior to the infusion, at the end of infusion, and 2 (± 1) hour safter the infusion. For subsequent bevacizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and within 30 minutes after completion of the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

Table 6 Schedule of Activities for Atezo + Bev Arm (cont.)

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[k] Laboratory tests must be performed within 96 hours prior to $dosing$ during the treatment period

[l] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits and at 3 months and 6 months after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[q] Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. See Table 5, for management guidelines for proteinuria.

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[t] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[u] On-treatment biopsies must be performed at least 7 days after the previous bevacizumab dose. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. The biopsy should not be performed in an anatomic location at risk for excessive bleeding, as determined by the investigator.

Table 6 Schedule of Activities for Atezo + Bev Arm (cont.)

[v] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[z] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

Table 6 Schedule of Activities for Atezo + Bev Arm (cont.)

[dd] Bevacizumab will be administered by IV infusion at a dose of 15mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 (± 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (± 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered ≥ 3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum), PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤ 30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + Bev = atezolizumab plus bevacizumab; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 19
Study Details Specific to Atezo + Bev + RTx Arm

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A19–1 BACKGROUND ON ATEZO + BEV + RTX ARM

A19–1.1 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets programmed death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed cell death protein 1 (PD-1) and B-lymphocyte activation antigen 1 (B7-1) (also known as cluster of differentiation 80 [CD80]), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and patients with cancer and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment.

Atezolizumab is approved for the treatment of urothelial carcinoma, non-small cell lung cancer (NSCLC), small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

A19–1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF) that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (mCRC) in combination with chemotherapy, as second-line colorectal cancer (CRC) treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crinò 2009).

In NSCLC, the Phase II/III Study E4599 showed that the addition of bevacizumab (15 mg/kg every three weeks [Q3W]) to the paclitaxel and carboplatin regimen led to a clinically relevant and statistically significant prolongation of overall survival (OS) (primary endpoint) compared with patients who were treated with paclitaxel and carboplatin alone (hazard ratio [HR] = 0.80; 95% CI: 0.69, 0.93; p = 0.003; Kaplan-Meier [KM]-estimated median: 12.3 months vs. 10.3 months). The OS benefit was supported by the results of progression-free survival (PFS) (HR = 0.65; 95% CI: 0.56, 0.76; KM-estimated median: 6.4 months vs. 4.8 months) and response rate (29.0% vs. 12.9%).

In addition, data from the protocol-defined final PFS (primary efficacy parameter) analysis of Study BO17704 (AVAIL; Roche Report No. 1023798) showed that the addition of bevacizumab (7.5 or 15 mg/kg Q3W) to cisplatin/gemcitabine chemotherapy resulted in a clinically relevant and statistically significant improvement in PFS (bevacizumab 7.5 mg/kg: HR = 0.75; 95% CI: 0.62, 0.91; p = 0.0026; KM-estimated median PFS: 6.7 months vs. 8.1 months) (bevacizumab 15 mg/kg: HR = 0.82; 95% CI: 0.68, 0.98; p = 0.0301; KM-estimated median PFS: 6.5 months vs. 6.1 months). Objective response rate (ORR) was also significantly increased in both bevacizumab-containing arms (7.5 mg/kg: 34.1% vs. 20.1%; bevacizumab 15 mg/kg: 30.4% vs. 20.1%).

Bevacizumab is currently being tested in combination with atezolizumab across different indications in Phase I, II, and III clinical studies.

A19–1.3 BACKGROUND ON RADIOTHERAPY AND OLIGOMETASTATIC DISEASE

A19–1.3.1 Nonclinical Evidence of Immune Re-Invigoration by Radiotherapy

A19–1.3.1.1 Radiotherapy in Checkpoint Inhibitor-Resistant Tumors

In tumors resistant to checkpoint inhibition, which is a rapidly growing segment clinically across disease sites, there is evidence that short bursts of radiation may modify the tumor microenvironment in nonclinical models. To this end, Wang el al. 2017, generated a nonclinical tumor model to study anti-PD-1 resistance by in vivo passaging of Kras-mutated, p53-deficient murine lung cancer cells ($p53^{R172H\Delta g/+}K\text{-}ras^{LA1/+}$) in a syngeneic host dosed repetitively with anti-mouse PD-1 antibodies leading to a highly resistant lung model. Interestingly, PD-L1 (CD274) expression did not differ between the

resistant and parental tumor cells. In contrast, major histocompatibility complex (MHC) class I and II, as well as β2-microglobulin, were significantly downregulated in the anti-PD-1-resistant tumors compared with parental tumors. Resistant tumors also contained fewer $CD8^+$ (CD8α) and $CD4^+$ tumor-infiltrating lymphocytes and reduced production of interferon (IFN)-γ. Localized flank radiotherapy induced IFN-β production, thereby elevating MHC class I expression on both parental and resistant tumor cells and restoring the responsiveness of resistant tumors to anti-PD-1 therapy.

A19–1.3.1.2 Role of Radiotherapy in (Oligo)Metastatic Disease

The definition of an oligometastatic state is in flux but essentially refers to a patient with a modest disease burden outside of the primary site. This state may consist of anywhere from 1-5 metastasis although some are willing to consider additional metastatic lesions as part of the oligometastatic state (Hellman and Weichselbaum 1995). The International Association for the Study of Lung Cancer recently published a consensus statement on the definition of oligometatstatic disease in NSCLC.
This expert panel agreed that the maximum number of metastases and organs involved depends on the possibility of offering a radical intent treatment strategy and thus, on the basis of the systematic review, a maximum of five metastases and three organs was agreed on. Importantly, the presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition (Dingemans et al. 2019).

In patients with a limited oligometastatic burden, emerging evidence suggests that treatment of all sites of disease with ablative therapies (such as surgery or stereotactic radiation) can improve patient outcomes, including OS and PFS.

Historically, evidence to support the oligometastatic state has consisted of single-arm, non-randomized studies without controls. One classic study reported on over 5000 patients with lung metastases from a variety of primary tumors. In patients who achieved a complete resection of their lung metastases, 5-year OS was 36%, better than might be expected for a cohort of patients with metastatic disease (Pastorino et al. 1997). Similarly, after radiation, a recent pooled analysis of 361 patients with oligometastatic lesions treated with radiation demonstrated a 3-year OS of 56% (Hong et al. 2018). The argument against the potential benefits of local therapies for this group of patients is based on selection of very fit patients with slow growing tumors, since randomized evidence to support the oligometastatic paradigm has been lacking (Primrose et al. 2010; Palma et al. 2014).

However, at least four recent randomized Phase II studies now provide some supporting evidence for the use of radiotherapy in an (oligo)metastatic state across various cancers offering a potential to support and improve drug development. Specifically, patients who have already progressed through current accepted checkpoint inhibitors (CPIs) face a grim prognosis with modest options available to them (please refer to Section A19–2.8).

A19–2 RATIONALE FOR ATEZO+BEV+RTX ARM

A19–2.1 THE PD-L1 PATHWAY

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

CIT agents, particularly immune CPIs, have made a significant impact on the treatment of patients with NSCLC in recent years. However, despite the remarkable clinical efficacy of these therapies, it has become clear that they are not sufficiently active for many patients.

A19–2.2 ANTI-VEGF CANCER TREATMENT

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that VEGF may reduce lymphocyte adhesion to vessel walls in the tumor microenvironment, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell (DC) function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2007).

In addition, VEGF recruits macrophages into the tumor microenvironment that have an M2 polarization state, which is typically involved in wound-healing. These M2 tumor-associated macrophages ultimately help establish and maintain an immunosuppressive microenvironment (Chen and Mellman 2013). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immune-modulatory antibody (anti-cytotoxic T lymphocyte–associated protein 4; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients.

A19–2.3 RADIOTHERAPY

A growing body of nonclinical work describes the immunogenic effects of radiation on the tumor microenvironment. Radiation can induce immunogenic cell death, local release of inflammatory cytokines, and damage associated molecular patterns (DAMPs) resulting in local effects on endothelial cell expression of adhesion receptors, increased immune cell trafficking, and immune cell activation (Rodriguez-Ruiz et al. 2017; Waldmann 2018).

However, radiation can also trigger effect within the tumor microenvironment that may be detrimental with regards to the development of anti-tumor immunity, including delayed increases in tumor infiltration by suppressive regulatory T cells as well as increased infiltration and activation of inhibitory macrophage and myeloid-derived suppressor cell lineages (Fridlender et al. 2009; Kachikwu et al. 2011; Tanaka et al. 2010; Tsai et al. 2007; Xu et al. 2013).

Dose, fractionation, and volume of radiation can influence immunologic effects in the tumor microenvironment. Nonclinical studies suggest that despite an initial local depletion of lymphocytes, hypofractionated regimens of radiation may be immune activating (Dewan et al. 2009). Additionally, recent work suggests that standard fractionation and hypofractionation induce expansion of unique immune populations with standard fractionation favoring a myeloid response and hypofractionation driving a lymphoid response that may be more favorable to adaptive anti-tumor immunity (Grapin et al. 2019).

Compared to high doses of radiation, which induce immunogenic cell death, dose-dependent increases of MHC-I and death receptors, e.g., Fas (Werner et al. 2017; Reits et al. 2006), moderate fractional doses of 3-10 Gy may be optimal for activating a type I IFN response in tumor cells via a dose-dependent increase in the cytoplasmic leakage of DNA from micronuclei, which activates the cyclic GMP-AMP

synthase/stimulator of interferon genes (cGAS/STING) pathway (Vanpouille-Box et al. 2017; Harding et al. 2017).

The activation of the cGAS/STING pathway is critical for the priming of tumor-specific CD8 T cells in the draining lymph nodes, but their expansion and effector function that is responsible for the rejection of the irradiated and non-irradiated metastases requires the addition of antibodies blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or PD-(L)1 (Vanpouille-Box et al. 2017).

At higher doses, radiation-induced STING activation may decline in part due to induced expression of Trex1 exonuclease, reducing the accumulation of cytoplasmic DNA resulting in negative feedback inhibition (Vanpouille-Box et al. 2017).

Another effect of low dose radiation (1-3 Gy), typically used in the clinic on a daily basis over 5-7 weeks, may be the modulation of the tumor microenvironment by ablating radiation-sensitive immune populations including suppressive and effector lymphocytes (Nakamura et al. 1990; Liu et al. 2010; Liu et al. 2015; Balogh et al. 2013). Both effects may create a window of opportunity to enhance response to immunotherapeutic agents, e.g., by locally and temporarily depleting exhausted and suppressive T cells from the tumor microenvironment and allowing reconstitution with a more favorable infiltrate using immunotherapies, and abscopal or systemic responses have been reported when radiotherapy has been combined with immunotherapy to produce or re-invigorate T cells that reject not only the irradiated tumor but also the metastases outside of the field of radiation (Demaria et al. 2015; Ngwa et al. 2018; Vanpouille-Box et al. 2015).

Thus, with regards to dose, the optimal fraction and number of fractions that provide the optimal milieu for induction of IFN-I, and the consequent activation of anti-tumor T cells, appears to range between 6 to 10 Gy per fraction, for most cancer cells, as below 6 Gy in some cancer cells the accumulation of DNA in the cytosol is suboptimal, while above a threshold of approximately 10 Gy the Trex1 exonuclease is induced with the above mentioned consequences. Moreover, it has been described recently that multi-fraction approaches may be superior to single fraction doses to further enhance the amplification of the IFN-I pathway and IFN-I production (Vanpouille-Box et al. 2017).

Besides dose and number of fractions, scheduling of radiotherapy also plays an important role. Dovide et al. (2014) demonstrated that dose scheduling is critical to the synergistic effect of combination therapy, with systemic CPI treatment administered within $\leq$7 days or less of the completion of radiotherapy generating effective anti-tumor immunity and long-term tumor control.

A19–2.4 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH BEVACIZUMAB

VEGF-A is a pro-angiogenic molecule produced by endothelium, tumors, and tumor-associated macrophages. The VEGF pathway also plays a crucial role in exerting and maintaining an immunosuppressive tumor microenvironment through several mechanisms. For example, VEGF-A inhibits the maturation of DCs (Gabrilovich et al. 1996), promotes the expression of inhibitory immune checkpoint molecules on intratumoral $CD8^+$ T-cells that express VEGF-R2 (Voron et al. 2015), and induces Fas ligand (FasL) expression on endothelial cells, which acquired the ability to kill effector $CD8^+$ T cells, but not regulatory T cells (Motz et al. 2014). Anti-VEGF agents such as bevacizumab are well known to promote the normalization of tumor vasculature and thereby increase access of therapeutic agents (Jain 2001). Furthermore, bevacizumab can restore and/or maintain the antigen-presentation capacity of DCs, leading to enhanced T-cell infiltration in tumors (Oelkrug and Ramage 2014; Wallin et al. 2016). Administration of anti–VEGF-A has been shown to attenuate tumor endothelial FasL expression and produce a significant increase in the influx of tumor-rejecting $CD8^+$ T cells, leading to tumor growth suppression (Motz et al. 2014). In addition, anti-VEGF therapies can reduce the frequency of myeloid-derived suppressor cells, decrease production of suppressive cytokines, and lower expression of inhibitory checkpoints on $CD8^+$ T cells in tumors (Roland et al. 2009; Voron et al. 2015). The immunomodulatory effect of bevacizumab is expected to increase $CD8^+$ T-cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

There is precedence for a beneficial effect of anti-angiogenesis in the context of immunotherapy. In a murine melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). High pretreatment serum VEGF was associated with poor survival following ipilimumab (anti-CTLA-4) monotherapy (Yuan et al. 2014), and synergistic effects were observed in a clinical study combining ipilimumab and bevacizumab, as shown by increased T-cell frequency in post-treatment biopsies, as well as marked increases in central memory cells in peripheral blood in the majority of patients (Hodi et al. 2014).

Furthermore, the anti-tumor activity of atezolizumab was increased in combination with bevacizumab, which was associated with a further increase in intra-tumoral $CD8^+$ T cells and increases in gene expression correlated with T-cell trafficking and tumor MHC-I expression and enhanced antigen-specific T-cell migration in metastatic RCC (Wallin et al. 2016).

The above-described data suggest that combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit for patients with non-squamous NSCLC.

A19–2.5 RATIONALE FOR COMBINING CANCER IMMUNE THERAPY WITH RADIOTHERAPY

Besides the immunogenic effects of radiation on the tumor microenvironment, i.e., the induction of immunogenic cell death, local release of inflammatory cytokines and DAMPs, which can result in increased immune cell trafficking and immune cell activation and thus potentially enhance the efficacy of immune-CPIs, it has been demonstrated that radiotherapy has the potential to convert the cancer into an in situ, individualized vaccine (Formenti and Demaria 2012; Demaria et al. 2005).

However, in established tumors, similarly to most cancer vaccines, radiotherapy by itself is insufficient to generate therapeutically effective anti-tumor immunity (Klebanoff et al. 2011), because of the established immunosuppressive micro-environment tumors have achieved at the time of detection and treatment (Vesely et al. 2011). Extensive experimental evidence indicates that radiotherapy can work in synergy with immunotherapy to generate T cells that reject not only the irradiated tumor but also the metastases outside of the field of radiation (Vanpouille-Box et al. 2015), which offers a rationale for utilizing radiation to enhance response to radiotherapy-immune CPIs in situations where tumors are unlikely to respond to immune-CPIs alone.

A19–2.6 RATIONALE FOR COMBINING ANTI-ANGIOGENIC THERAPY WITH RADIOTHERAPY

The enhanced effect of a combinatorial approach using radiotherapy and anti-angiogenic treatment has been demonstrated in multiple clinical studies (Mauceri et al. 1998; Teicher et al. 1994; Teicher et al. 1995), with vessel normalization induced by anti-angiogenic drugs being one of the potential explanations for enhanced efficacy of the combination. However, the beneficial effects of combining radiotherapy with anti-angiogenic agents could also be demonstrated when radiotherapy was administered before the systemic treatment with anti-angiogenic agents (Kleibeuker et al. 2015). This could be in part explained by the stimulation of angiogenesis by irradiation by inducing the expression of pro-angiogenetic growth factors like VEGF by cancer cells or other cells that reside in the tumor microenvironment (Kleibeuker et al. 2016; Chuang et al. 2002; Feng et al. 2015; Solberg et al. 2008). Sofia Vala et al. (2010) demonstrated that low dose irradiation induces VEGF signaling in endothelial cells, while Meng et al. (2010) demonstrated increased VEGF expression of macrophages in the stromal tissue after irradiation.

These findings suggest that ionizing radiation can enhance tumor perfusion by induction of a pro-angiogenic response which can be counteracted by anti-angiogenesis treatment (Kleibeuker et al. 2016).

A19–2.7 CLINICAL STUDIES OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB

Study GP28328 is an ongoing, Phase Ib, open-label, multicenter study combining atezolizumab (1200 mg Q3W) with bevacizumab (15 mg/kg Q3W) in patients with advanced solid tumors, with expansion arms for patients with RCC, mCRC, gastric cancer, and ovarian cancer. Safety findings have been consistent with the known single-agent safety profiles for each drug; no new safety signals have been identified. The regimen has been well tolerated, and adverse events have been manageable. Another Phase Ib, open-label, multicenter study (GO30140) is investigating a similar dose of atezolizumab combined with bevacizumab in patients with hepatocellular carcinoma. In addition, this combination is being tested in a Phase II randomized study (WO29074) in which atezolizumab is administered as monotherapy or in combination with bevacizumab, compared with sunitinib, in patients with untreated advanced RCC.

In chemotherapy-naive patients with Stage IV NSCLC, results from Phase III Study GO29436 (IMpower150) have shown that atezolizumab in combination with carboplatin + paclitaxel and bevacizumab results in significantly longer OS compared to carboplatin + paclitaxel and bevacizumab alone (Socinski et al. 2018). For inoperable, locally advanced, or metastatic RCC, Phase III Study WO29637 (IMmotion151) demonstrated improved PFS after treatment with the combination of atezolizumab plus bevacizumab compared with sunitinib treatment in treatment-naive patients (Motzer et al. 2018). Phase Ib Study GO30140 in hepatocellular carcinoma front line found an ORR of 65% in 23 evaluable patients, across etiology, geography, baseline alpha feta protein levels, and extrahepatic spread. The combination is currently being explored in a randomized Phase III study YO40245 (IMbrave150) versus sorafenib in first-line treatment for hepatocellular carcinoma (Stein et al. 2018). These are examples of clear synergy between atezolizumab and bevacizumab in different tumor types, which support further exploration of the combination in NSCLC.

Detailed clinical study results for atezolizumab and bevacizumab can be found in the Atezolizumab Investigator's Brochure and the Bevacizumab Investigator's Brochure, respectively.

A19–2.8 CLINICAL EVIDENCE SUPPORTING LOCAL RADIOTHERAPY IN METASTATIC DISEASE

A multitude of trials have explored the utility and effectiveness of local therapy, two of which were performed in the setting of metastatic NSCLC. In both, patients presented with a primary lung tumor and a limited number of metastatic lesions (1-3 in one study,

1-5 in the other study), and after initial systemic therapy, patients were randomly assigned to standard palliative treatments vs. consolidative ablative treatments to all sites of disease. Both studies were halted early due to evidence of efficacy, with the ablative treatments achieving a ~3-fold improvement in PFS (Iyengar et al. 2018; Gomez et al. 2016). Follow-up results with longer follow-up continued to demonstrate the benefits of local consolidative therapy in this oligometastatic setting (Gomez et al. 2019). Based on these results, the Phase III NRG LU-002 study is assessing the impact of consolidative ablative therapies on OS.

Finally, Palma et al. (2019), reported the results of a multi-institutional prospective study in patients with oligometastatic disease (up to five metastases) testing stereotactic body radiotherapy (SBRT): long term follow-up reported a statistically significant improvement in PFS and OS. The study used ablative radiotherapy with different doses and fractionations, but with the exception of the doses used when the spinal cord is in the field (7GyX5, 35 GY total dose), all fractionation schemas used achieved a biologically equivalent dose $\geq$100 Gy. Toxicities overall were modest;however, there were ~4% Grade 5 toxicity reported. Additional reviews of the safety of combined ablative SBRT and immunotherapy further confirm the overall safety of this combination (Verma et al, 2018).

Recently, Theelen et al. (2019) reported the results of a multicenter, Phase 2 randomized clinical study, assessing safety and efficacy of Pembrolizumab (200 mg/kg every 3 weeks) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) in 92 patients with advanced NSCLC, not limited to patients with oligometastatic disease. A total of 76 patients were randomized to the control arm (n = 40) or the experimental arm (n = 36). The ORR at 12 weeks was 18%in the control arm versus 36%in the experimental arm (p = 0.07). Median PFS was 1.9 months (95% CI: 1.7, 6.9 months) versus 6.6 months (95% CI: 4.0, 14.6 months) (HR = 0.71; 95% CI: 0.42, 1.18; p = 0.19), and median OS was 7.6 months (95% CI: 6.0, 13.9 months) versus 15.9 months (95% CI: 7.1 months to not reached) (HR = 0.66; 95%CI: 0.37, 1.18; p = 0.16). In this study, the safety profile observed was consistent with previous studies of pembrolizumab treatment for advanced NSCLC (Herbst et al. 2016; Reck et al. 2016; Garon et al. 2015). Most immune-mediated events were Grade 1 or 2 and no significant differences in were seen with regards to safety between arms. The investigators reported that 1 patient experienced an immune-related adverse event that may have been augmented by SBRT: this patient developed nephritis after the administration of SBRT on a retroperitoneal lesion and the third course of pembrolizumab, resulting in discontinuation of treatment.

Furthermore, Luke et al. (2018) reported data on 73 patients with solid tumors from a Phase I study treated with pembrolizumab monotherapy after ablative SBRT to 2 to

4 tumor lesions. While the timing of SBRT was similar to the study conducted by Theelen et al. (2019), doses varied from 30 to 50 Gy in 3 to 5 fractions, depending on the tumor site. In this study, Response Evaluation Criteria in Solid Tumors (RECIST)-based ORR was 13.2% in a population of heavily pretreated patients. Of note, the population was unselected for PD-L1 expression, consisted of 27 cancer types, and was enriched in histologies not associated with significant responses to pembrolizumab. The most common treatment related adverse events were general disorders and administration site conditions (n = 7), followed by gastrointestinal disorders (n = 6). The authors also concluded that the administration of SBRT before pembrolizumab treatment was well tolerated.

A19–2.9 BENEFIT–RISK ASSESSMENT

Metastatic NSCLC remains an incurable disease with a high unmet medical need, especially in the CPI-pretreated patient population. Because of the reinvigoration of an anti-tumor immune response by immune-modulating SBRT (I-SBRT) and the potential synergism with immune-CPI treatment, the potentially synergistic mechanisms of action of atezolizumab and bevacizumab, as well as their manageable and tolerable safety profiles (see Section A19–5), combination treatment with these two treatment modalities appears to have promising therapeutic potential in solid tumors and may reinvigorate and augment the anti-tumor immune response, potentially resulting in improved and more durable clinical benefit for patients with NSCLC.

For the evaluation of the impact of the COVID-19 pandemic on the benefit–risk assessment, please refer to Section 1.4.

A19–3 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV + RTX ARM

A19–3.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is an approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A19–3.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered by infusion at a fixed dose of 15 mg/kg Q3W (15 mg/kg on Day 1 of each 21-day cycle) in combination with atezolizumab. This dose

and schedule was selected on the basis of both nonclinical studies and available clinical data and are the doses recommended for use for indications in which bevacizumab is approved. Furthermore, these doses have been previously tested in combination with atezolizumab demonstrating tolerability without exacerbation of bevacizumab or atezolizumab-associated adverse events (refer to the Bevacizumab and Atezolizumab Investigator Brochure for further details).

A19–3.3 RATIONALE FOR RADIOTHERAPY DOSE AND SCHEDULE

A large number of clinical studies are ongoing to test the ability of radiotherapy to improve tumor immunogenicity and enhance responses to immune checkpoint blockade (Kang et al. 2016). As mentioned earlier, laboratory data and emerging clinical data support a rationale of both targeting multiple metastatic sites and administering radiotherapy regimens with single or fractionated non-ablative SBRT (I-SBRT) (Theelen et al. 2019). To minimize potential toxic effects caused by the addition of radiotherapy and yield optimal immunologic priming in this CPI-experienced patient population, based on emerging data on the relevance of dose per fraction to best induce IFN-I, a non-ablative dose of 8 Gy x 3 fractions, delivered approximately every other day to each metastatic site up to 5 sites has been chosen. To further reduce the possibility of toxic effects, I-SBRT has to be administered sequentially rather than concurrently with systemic therapy, with no longer than seven days between the last radiotherapy dose and the first dose of atezolizumab + bevacizumab to minimize delay of systemic treatment. Constraints to normal tissue, will follow, based on the technical requirements in part defined by NRG-BR001, the first National Cancer Institute-sponsored study of SBRT for the treatment of multiple metastases (Al-Hallaq et al. 2016).

A19–4 MATERIALS AND METHODS SPECIFIC TO ATEZO + BEV + RTX ARM

A19–4.1 SYSTEMIC TREATMENT IN ATEZO + BEV + RTX ARM

A19–4.1.1 Formulation, Packaging, and Handling

A19–4.1.1.1 Atezolizumab

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A19–4.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile solution in a single-use, 4-mL or 16-mL, preservative-free glass vial. The 4-mL vial contains 100 mg

of bevacizumab (25 mg/mL), and the 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

For information on the formulation, and handling of bevacizumab, refer to the pharmacy manual and the Bevacizumab Investigator's Brochure

A19–4.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Bev + RTx arm will receive systemic treatment as outlined in Table 1 until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 3.1.1 for details). It is mandated that systemic treatment be initiated no later than 7 days after completion of radiotherapy.

Table 1 Treatment Regimen for Atezo + Bev + RTx Arm

Radiotherapy	
Treatment Duration	Dose and Fractionation
Up to 21 days (±5 days, including simulation, contouring, and planning)	8Gy x 3
Systemic Therapy	
Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy.

Any overdose or incorrect administration of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF. No safety data related to overdosing of atezolizumab or bevacizumab are available.

A19–4.1.2.1 Bevacizumab Administration

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg on Day 1 of each 21-day cycle.

Administration of bevacizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Bevacizumab infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Bevacizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the bevacizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) should be measured within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (±15) minutes. • Vital signs should be measured at the end of infusion and 2 (±1) hours after the infusion. • Patients should be informed about the possibility of delayed postinfusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an infusion-related reaction, or 90 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. • Vital signs should be measured within 30 minutes after completion of the infusion.

No dose modification for bevacizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A19–5.1.6. Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A19–4.1.2.2 Atezolizumab Administration

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5. Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during and 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) for atezolizumab are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for atezolizumab treatment interruption or discontinuation because of toxicities are provided in Section A19–5.1.6. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

A19–4.1.3 Radiotherapy Administration

Patients in the Atezo + Bev + RTx arm will receive stereotactic radiotherapy as outlined in the technical radiotherapy manual. Radiotherapy phase starts once a patient is randomized to the Atezo + Bev + RTx Arm and signed the arm specific informed consent. It includes I-SBRT simulation, contouring, and planning followed by I-SBRT administration. *If a patient is randomized to the Atezo + Bev + RTx arm but cannot start treatment with radiotherapy for clinical/technical reasons (e.g., contraindication for radiotherapy that is detected after randomization, e.g., during the radiotherapy*

planning process), this patient will be allowed to skip radiotherapy and start treatment with Atezo + Bev. The reason for skipping radiotherapy will be documented accordingly.

Radiotherapy will be delivered with four major guiding principles:

- The goal of the protocol is to use SBRT to optimize the response to immunotherapy
- In order to minimize toxicity, non-ablative SBRT doses will be used and normal tissue tolerance doses will never be exceeded.
- In order to avoid delays in subsequent systemic therapy, all SBRT will be delivered over the course of 21 days (±5 days)
- There are many techniques that facilitate the safe application of SBRT, each center will be able to continue to use their preferred technique.

Please refer to the technical radiotherapy manual for further details on the radiotherapy treatment regimen.

A19–4.1.4 Stage 2 Treatment

Patients in Stage 1 who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1) or unacceptable toxicity related to bevacizumab will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 4, provided they meet eligibility criteria (see Section 4.1) and the arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit or unacceptable toxicity. It is recommended that patients begin Stage 2 treatment as soon as possible. Tumor assessments performed prior to or at the time of loss of clinical benefit or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

Table 4 Stage 2 Treatment Regimens Available for the Atezo + Bev + RTx Arm

Study Treatment	Appendix
Atezo + Docetaxel	Appendix 16
Atezo + Lina	Appendix 17

Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy;
Atezo = atezolizumab; Lina = linagliptin.

Refer to Appendix 16 and Appendix 17 for details specific to the atezolizumab plus docetaxel arm and atezolizumab plus linagliptin arm, respectively.

A19–4.2 CONCOMITANT THERAPY FOR ATEZO + BEV + RTX ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of any study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

A19–4.2.1 Permitted Therapy for Atezo + Bev + RTx Arm

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Inactivated *vaccines (such as* influenza *and COVID-19)*

  Live, attenuated vaccines are not permitted (see A19–4.2.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Treatment with atezolizumab may be continued during palliative radiotherapy.
- Prophylactic treatment of asymptomatic metastasis, unless at risk for an impending clinical event such as cord compression or pathologic fractions, is not allowed in this arm.

Radiotherapy to the brain as outlined below:

Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) provided that all of the following criteria are met:

- The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.
- The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

  Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy must be discontinued from study treatment.
- Anti-convulsant therapy, if required, is administered at a stable dose.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab and bevacizumab infusions only, at the discretion of the investigator.

Anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors are not to be administered prophylactically prior to the first doses of systemic study treatment. However, at the discretion of the investigator, anti-emetic medications, anti-diarrheal medications, and hematopoietic growth factors may be administered prophylactically per standard local practice before the second and subsequent doses of systemic study treatment.

In general, investigators should manage a patient's care (including preexisting conditions) with therapies other than those defined as cautionary or prohibited therapies (see Sections A19–4.2.2 and A19–4.2.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

At this time there is no evidence to suggest an interaction between the COVID-19 vaccines and bevacizumab. Based on the mechanism of action of bevacizumab, an interaction with the COVID-19 vaccines is unlikely. COVID-19 vaccines must be given in accordance with the approved/authorized vaccine label and official immunization guidance. The decision of administration of a COVID-19 vaccine to a

patient should be made on an individual basis by the investigator in consultation with the patient.

A19–4.2.2 Cautionary Therapy for Atezo + Bev + RTx Arm

A19–4.2.2.1 Corticosteroids and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. *The Medical Monitor is available to advise as needed.*

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Appendix 6 for details).

The above list of cautionary medications is not necessarily comprehensive.
The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the Medical Monitor *is available to advise as needed* if questions arise regarding medications not listed above.

A19–4.2.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A19–4.2.3) may be used during the study at the discretion of the investigator.

A19–4.2.3 Prohibited Therapy for Atezo + Bev + RTx Arm

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, may be prohibited prior to starting any study treatment, depending on the agent (see Section 4.1.2), and is prohibited during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and radiotherapy to the brain under circumstances outlined in Section A19–4.2.1.
- Investigational therapy is prohibited within 28 days prior to initiation of any study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of systemic study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of systemic study treatment and during systemic study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (>325 mg/day) or clopidogrel (> 75 mg/day) or equivalent is prohibited.

A19–4.3 CONTRACEPTION REQUIREMENTS FOR ATEZO + BEV + RTX ARM

Contraception requirements for women and men in the Atezo + Bev arm are outlined below:

- Women of childbearing potential must agree to refrain from donating eggs and to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 5 months after the last dose of atezolizumab, for 6 months after the last dose of bevacizumab, and for at least 6 months after the last dose of radiotherapy

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of bevacizumab and for at least 6 months after the last dose of radiotherapy to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

A19–4.4 QUALITY ASSURANCE

A19–4.4.1 Quality Assurance for Morpheus Sites

Prior to opening the arm, each participating site will be required to send a benchmark treatment plan to the Medical Monitor, to ensure that the treatment plans are designed in compliance with the protocol. The Sponsor will provide computed tomography (CT) datasets as a basis for the benchmark treatment plan. Furthermore, the Sponsor will collect anonymized radiotherapy treatment plans for each patient.

A19–5 ASSESSMENT OF SAFETY FOR ATEZO + BEV + RTX ARM

A19–5.1 SAFETY PLAN FOR ATEZO + BEV + RTX ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and bevacizumab as well as I-SBRT (Theelen et al. 2019) in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A19–5.1.1, A19–5.1.2, A19–5.1.3, A19–5.1.4, and A19–5.1.5). Guidelines for management of patients who experience specific adverse events related to

atezolizumab and/or bevacizumab are provided in Section A19–5.1.6. The management of potential I-SBRT related adverse events will be performed as per institutional guidelines.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study treatment will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

To further reduce the possibility of toxic effects by the addition of radiotherapy, the treatments will be administered sequentially instead of concurrently, with I-SBRT preceding systemic treatment.

Adverse events will be reported as described in Sections 5.2–5.6.

A19–5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A19–5.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: gastrointestinal perforations, hemorrhage, arterial thromboembolic events, fistulae, wound-healing complications, hypertension, venous thromboembolism, and proteinuria.

Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of anticipated safety risks for Bevacizumab.

A19–5.1.3 Risks Associated with Combination Use of Atezolizumab and Bevacizumab

On the basis of the frequency of adverse events associated with either atezolizumab or bevacizumab, the following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and bevacizumab: cardiovascular, gastrointestinal, renal, and pulmonary toxicity.

A19–5.1.4 Risks Associated with Combination Use of SBRT and Checkpoint-Inhibitors

Recently, Theelen et al. (2019). reported the results of a multicenter, Phase II randomized clinical study, assessing safety and efficacy of pembrolizumab (200 mg/kg every 3 weeks) either alone (control arm) or after radiotherapy (3 doses of 8 Gy) in 92 patients with advanced NSCLC. In this study, the safety profile observed was consistent with previous studies of pembrolizumab treatment for advanced NSCLC (Herbst et al. 2016; Reck et al. 2016; Garon et al, 2015). Most immune-mediated events were Grade 1 or 2, and the most common adverse events were fatigue (28 of 72 patients [39%]), flu-like symptoms (23 of 72 [32%]), and cough (20 of 72 [28%]). There were no significant differences between the arms at the alpha = 0.1 level, except fatigue (10 of 37 patients [27%] vs. 18 of 35 [51%]; p = 0.05) and pneumonia (3 of 37 [8%] vs. 9 of 35 [26%]; p = 0.06). However, after applying the Holms-Bonferroni correction to compensate for the number of different adverse events categories compared, no significance differences between arms remained. Grade 3 to 5 pembrolizumab-related toxic effects were reported in 12 patients (17%), with no significant differences between arms. The investigators reported that 1 patient experienced an immune-related adverse event that may have been augmented by I-SBRT:

> This patient developed nephritis after the administration of SBRT on a retroperitoneal lesion and the third course of pembrolizumab, resulting in discontinuation of treatment.

A19–5.1.5 Risks Associated with Combination Use of Radiotherapy and Bevacizumab

Pulmonary hemorrhage/hemoptysis potentially related to bevacizumab has been observed primarily in studies in patients with NSCLC. Prior radiotherapy has been identified as a possible risk factor for this adverse event, while other risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors prior to or during therapy.

In Study AVF2119g in patients with metastatic breast cancer, there was a slight increase in the incidence of congestive heart failure or cardiomyopathy in the combination arm (3.1% vs. 0.9%). Prior anthracycline exposure and prior chest wall radiation may increase the risk of congestive heart failure in patients receiving bevacizumab (Miller et al. 2005).

Study AVF2941n (BRiTE) was a registry of 1953 patients with mCRC in the United States who were treated with a bevacizumab-containing regimen as their first-line therapy. The study evaluated the incidences of gastrointestinal perforation, Grade ≥ 3

bleeding events; post-operative bleeding and wound healing complications, arterial thrombotic events, and other bevacizumab-related serious adverse events. Subgroup analyses of this study showed that patients with primary tumor intact, recent prior history of sigmoidoscopy or colonoscopy, or prior adjuvant radiotherapy appeared to have a slightly higher incidence of gastrointestinal perforation (Hedrick et al. 2006).

A19–5.1.6 Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm

A19–5.1.6.1 Dose Modifications for Systemic Treatment

There will be no dose modifications for atezolizumab or bevacizumab in this study.

A19–5.1.6.2 Systemic Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment (see Table 5). If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for > 42 days if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with bevacizmab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

If either study drug is discontinued, the other study drug can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

Refer to Section A19–4.1.2 for information on dose interruptions for reasons other than toxicity.

A19–5.1.6.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Table 5. *These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.*

Of note, the management of potential I-SBRT related adverse events will be performed as per institutional guidelines.

Table 5 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Bev + RTx Arm

Event	Action to Be Taken
IRRs, *CRS,* anaphylaxis, and hypersensitivity reaction	
General guidance	• Guidelines for management of IRRs *and CRS* for atezolizumab are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and bevacizumab.
IRR to bevacizumab, Grade 1	• Reduce infusion rate to ≤50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 2	• Reduce infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgment. • If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.
IRR to bevacizumab, Grade 3–4	• Stop infusion. • Discontinue bevacizumab.

CRS = cytokine-release syndrome; IRR = infusion-related reaction.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity	
General guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug-induced effects. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. • Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: <u>Medication</u> – Initiate loperamide (4 mg) every 6 hours around the clock, alternating with diphenoxylate hydrochloride (5 mg)/atropine sulfate (0.5 mg) every 6 hours around the clock, until no loose stools for 24 hours. – If Grade ≥2 diarrhea persists after 48 hours of treatment with loperamide and diphenoxylate/atropine, consider initiating second-line agents (e.g., octreotide, budesonide, tincture of opium). <u>Oral Supplementation</u> – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥1 diarrhea or vomiting. <u>Dietary Modifications</u> – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade).

CRP = C-reactive protein; GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 1 or Grade 2 (tolerable)	• Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate.
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

CRP = C-reactive protein; GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and bevacizumab. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for >7 days.

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 2	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] Bevacizumab may continue at the discretion of the investigator per medical judgment. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Gastrointestinal perforation, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Initiate treatment per institutional guidelines.
Bowel obstruction, Grade 2	• Hold bevacizumab for partial obstruction requiring medical intervention. Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • Bevacizumab may be restarted upon complete resolution of event.

GI = gastrointestinal; NSAIDs = non–steroidal anti-inflammatory drugs.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Bowel obstruction, Grade 3–4	• Hold bevacizumab for complete obstruction. Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. • If surgery is necessary, patient may restart bevacizumab after full recovery from surgery and at investigator's discretion.
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Continue atezolizumab and bevacizumab. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For Grade 2 rash, consider referral to dermatologist. Acneiform rash: • Consider initiating treatment with topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 3	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 2 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6 • Withhold bevacizumab. • If event resolves to Grade 1 or better, resume bevacizumab. • Permanently discontinue bevacizumab if withheld for > 42 days or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.
Pulmonary event, Grade 1	• Continue atezolizumab and bevacizumab. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.* • For recurrent pneumonitis, treat as a Grade 3 or 4 event.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 2	• Withhold atezolizumab. Bevacizumab may continue at the discretion of the investigator per medical judgment • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Bevacizumab may continue at the discretion of the investigator per medical judgment. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with *corticosteroids equivalent to* 1−2 mg/kg/day *IV methylprednisolone*. • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab.
Asymptomatic hyperthyroidism	TSH ≥0.1 mU/L and <0.5 mU/L: • Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab. TSH <0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Hyperglycemia, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Continue bevacizumab.
Hypophysitis (pan-hypopituitarism), Grade 2, 3 ,or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment
Amylase and/or lipase elevation, Grade 3 or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Pancreatitis, Grade 2, 3 , or 4	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Neurologic disorder	
Neuropathy, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Bevacizumab may continue at the discretion of the investigator per medical judgment.
Myasthenia gravis or Guillain-Barré syndrome, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Neurologic disorder (cont.)	
Immune-related meningoencephalitis, any grade	• Follow guidelines for atezolizumab in Appendix 6. • Withhold bevacizumab. • If patient stabilizes within 42 days, resume bevacizumab.
Ocular toxicity	
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 1	• Continue atezolizumab and bevacizumab. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 2	• Withhold atezolizumab. Continue bevacizumab. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]
Potential immune-related ocular toxicity (e.g., uveitis, retinal events), Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] Bevacizumab may continue at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Hypertension	
General guidance	• Grade 2 or above, start antihypertensive therapy.
Hypertension Grade 2	• Hold bevacizumab. [a] Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b] • Once blood pressure <140/90 mmHg, patient may continue bevacizumab therapy.
Hypertension Grade 3	• If blood pressure is not controlled to 140/90 mmHg with medication, discontinue bevacizumab • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]
Hypertension Grade 4	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment. [b]

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Hemorrhage	
Hemorrhage, Grade 1 (excluding cerebral hemorrhage)	<u>All patients:</u> • Continue atezolizumab. <u>Patients not receiving full-dose anticoagulation:</u> • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. [a] • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] <u>Patients receiving full-dose anticoagulation:</u> • Permanently discontinue bevacizumab. [a]

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Hemorrhage, Grade 2 (excluding cerebral hemorrhage)	<u>All patients:</u> • Continue atezolizumab. <u>Patients not receiving full-dose anticoagulation:</u> • Withhold bevacizumab. • If the bleeding resolves, hemoglobin levels are stable, there is no bleeding diathesis, and there is no anatomic or pathologic condition that would significantly increase the risk of hemorrhage recurrence ≤ 56 days after event onset, resume bevacizumab. If not, permanently discontinue bevacizumab. a • For recurrent pulmonary or CNS (including intracranial) hemorrhage events, permanently discontinue bevacizumab. [a] <u>Patients receiving full-dose anticoagulation:</u> • Permanently discontinue bevacizumab. [a]
Grade 3 hemorrhage (excluding cerebral hemorrhage)	• Discontinue bevacizumab. • Continue atezolizumab.
Grade 4 hemorrhage or any grade cerebral hemorrhage	• Discontinue bevacizumab and atezolizumab. [a]

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Venous thromboembolic events	
Venous thromboembolic event Grade ≥3	• For Grade 3 thromboembolic events, hold bevacizumab for >3 weeks. Bevacizumab treatment may be resumed during the period of therapeutic-dose anticoagulant therapy once the level of anticoagulation therapy is stabilized: • Anticoagulant treatment should be administered per institutional guidelines. • After administration of bevacizumab is restarted, if the patient experiences another Grade ≥3 venous thromboembolic event, bevacizumab should be discontinued. • For Grade 4 thromboembolic events, discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Arterial thromboembolic events	
Arterial thromboembolic event, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Proteinuria	
Proteinuria first occurrence, no diagnosis of nephrotic syndrome	• No bevacizumab dose interruptions for proteinuria < 2 + by dipstick. • For proteinuria 2 + or 3 + by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤ 2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria > 2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤ 2 g/24 hours. • When proteinuria has decreased to ≤ 2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤ 1 g/24 hours. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by both the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Proteinuria (cont.)	
Proteinuria second and subsequent occurrences, no diagnosis of nephrotic syndrome	• No bevacizumab dose interruptions for proteinuria <3+ by dipstick. • For proteinuria 3+ by dipstick, administer bevacizumab as planned and collect 24-hour urine for determination of total protein within 3 days before next scheduled bevacizumab administration. • If 24-hour proteinuria ≤2 g, the next bevacizumab dose can be administered as scheduled. • If 24-hour proteinuria >2 g, hold bevacizumab treatment. Continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose, and continue to hold scheduled bevacizumab until proteinuria has decreased to ≤2 g/24 hours. • When proteinuria has decreased to ≤2 g/24 hours, scheduled bevacizumab may be administered as planned. However, continue to do 24-hour urine collections for determination of total protein within 3 days of each scheduled bevacizumab dose until proteinuria has improved to ≤1 g/24 hr. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Proteinuria with diagnosis of nephrotic syndrome	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Fistula	
Tracheoesophageal fistula, any grade	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Fistula (non- tracheoesophageal), Grade 4	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Wound dehiscence	
Wound dehiscence, any grade requiring medical or surgical therapy	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Table 5 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Bev + RTx Arm (cont.)

Event	Action to Be Taken
Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome	
PRES/RPLS, any grade confirmed by MRI	• Discontinue bevacizumab. • Atezolizumab may continue without interruption at the discretion of the investigator per medical judgment.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Interrupt dosing of attributable study drug at the discretion of the investigator. During this time, treatment may continue with non-attributable study drugs. • If bevacizumab is the attributable study drug and the event resolves to Grade ≤1 within 42 days, then resume bevacizumab at fixed dose. If not, permanently discontinue bevacizumab. • If atezolizumab is the attributable study drug and the event resolves to Grade ≤1 within 12 weeks, then resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c]

PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

A19–5.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV + RTX ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Bev arm are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ upper limit of normal
- Systemic lupus erythematosus
- Neurologic disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, and hemophagocytic lymphohistiocytosis or macrophage activation syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

- Grade ≥3 hypertension
- Grade ≥3 proteinuria
- Any grade gastrointestinal perforation, abscesses, or gastrointestinal fistulae
- Grade ≥2 non-gastrointestinal fistula or abscess
- Grade ≥3 wound-healing complication
- Any grade CNS bleeding
- Grade ≥2 hemoptysis
- Other grade ≥3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome (PRES)
- Grade ≥3 congestive heart failure

A19–5.3 REPORTING REQUIREMENTS FOR PREGNANCIES IN ATEZO + BEV + RTX ARM

A19–5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, or 6 months after the last dose of radiotherapy. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

A19–5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab or within 6 months after the last dose of radiotherapy. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee

immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A19–5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A19–5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A19–6 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + BEV + RTX ARM

Table 6 Schedule of Activities for Atezo + Bev + RTx Arm

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Radiotherapy Phase Day 1 to 21 (±5 days)	Treatment Cycles (21-Day Cycles) [a] Cycle 1 [b] Day 1	Treatment Cycles (21-Day Cycles) [a] Cycles ≥2 Day 1 (±3 days)	Stage 2 Screen. (see Appendix 2) [c] or Treatment Discontinuation [d] (see below)	Follow-Up [d] Every 3 Months (±7 days)
Molecular profile of lung cancer (if available)	See Appendix 2		Whenever updated information becomes available			
Vital signs [e]			x	x	x	
Weight [f]			x	x	x	
Complete physical examination [g]					x	
Limited physical examination [f, h]			x	x		
ECOG Performance Status [f]			x	x	x	
ECG [f, i]			Perform as clinically indicated			
Hematology [j]			x [k, l]	x [k]	x	
Chemistry [m]			x [k, l]	x [k]	x	
Coagulation (INR and aPTT)			x [k]			
TSH, free T3 (or total T3), and free T4 [n]			x [l]		x	
Pregnancy test [o]			x	x	x	
Urinalysis [p]			x	x [q]	x	

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

Assessment/Procedure	Stage 1 Screening Days –28 to –1	Radiotherapy Phase Day 1 to 21 (±5 days)	Treatment Cycles (21-Day Cycles) [a] Cycle 1 [b] Day 1	Treatment Cycles (21-Day Cycles) [a] Cycles ≥2 Day 1 (±3 days)	Stage 2 Screen. (see Appendix 2) [c] or Treatment Discontinuation [d] (see below)	Follow-Up [d] Every 3 Months (±7 days)
Blood sample for blood-based NGS ctDNA test	See Appendix 2				x	
Serum autoantibody sample [r]			Perform if a patient experiences a suspected immune-mediated adverse event			
PK samples			Refer to Table 7			
ADA samples			Refer to Table 7			
Biomarker samples			Refer to Table 7			
Blood sample for RBR (optional) [s]			x			
Tumor biopsy			x [t, u]			
Tumor biopsy (optional)			x [u, v]			
Tumor response assessments			x [w, x, y]			
Concomitant medications [z]			x	x	x	
Adverse events [aa]			x	x	x [aa]	x [aa]
Atezolizumab administration [bb, cc]			x	x		
Bevacizumab administration [cc, dd]			x	x		
I-SBRT planning [ff]		x [gg]				
I-SBRT administration 3x8GY [ff]		x				

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

Assessment/Procedure	Stage 1 Screening	Radiotherapy Phase	Treatment Cycles (21-Day Cycles) [a]		Stage 2 Screen. (see Appendix 2) [c] or Treatment Discontinuation [d] (see below)	Follow-Up [d]
			Cycle 1 [b]	Cycles ≥2		Every 3 Months (±7 days)
	Days –28 to –1	Day 1 to 21 (±5 days)	Day 1	Day 1 (±3 days)		
Survival follow-up and anti-cancer treatment	See Appendix 2					x [ee]

ADA = anti-drug antibody; Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy; CT = computed tomography; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FDG = fluorodeoxyglucose; I-SBRT = immune-modulating stereotactic body radiotherapy; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PET = positron emission tomography; PK = pharmacokinetic; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; Screen = screening.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window. *The Medical Monitor is available to advise as needed.*

[b] It is recommended that treatment be initiated no later than 7 days after completion of radiotherapy.

[c] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Section 3.1.3) and will undergo screening assessments to determine eligibility. Study details specific to the Stage 2 treatment regimens are provided in the appropriate appendix. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[d] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of systemic study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Treatment discontinuation assessments must be performed for all patients, regardless of whether they enter Stage 2. Patients who do not enter Stage 2 will then undergo follow-up assessments.

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

[e] Vital signs include respiratory rate, pulse rate, pulse oximetry, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of atezolizumab, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent atezolizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion. For the first infusion of bevacizumab, vital signs should be measured within 60 minutes prior to the infusion, at the end of the infusion, and 2 (±1) hours after the infusion. For subsequent bevacizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and within 30 minutes after completion of the infusion.

[f] *Assessment may be performed within 24 hours prior to dosing during the treatment period.*

[g] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] It is recommended that patients be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[k] Laboratory tests must be performed within 96 hours prior to *dosing* during the treatment period

[l] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and AST. Amylase and lipase will be included at Day 1 of each treatment cycle.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] All women of childbearing potential will have a serum pregnancy test at Stage 1 screening. Urine or serum pregnancy tests will be performed at specified subsequent visits and at 3 months and 6 months after the last dose of systemic study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

[q] Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. See Table 5 for management guidelines for proteinuria.

[r] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti–neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody.

[s] Not applicable for a site that has not been granted approval for RBR sampling. Perform only for patients at participating sites who have provided written informed consent to participate.

[t] Patients will undergo tumor biopsy sample collection at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled in the mandatory serial biopsy arm at sites that have been granted approval for mandatory serial biopsies (see Section 3.1.2) will undergo tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible). See Section 4.5.8 for tissue sample requirements.

[u] On-treatment biopsies must be performed at least 7 days after the previous bevacizumab dose. Bevacizumab must be administered ≥3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated. The biopsy should not be performed in an anatomic location at risk for excessive bleeding, as determined by the investigator.

[v] Consenting patients will undergo optional tumor biopsy sample collection 4 weeks (±7 days) after treatment initiation (if deemed clinically feasible) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 48 weeks following treatment initiation, and every 12 weeks (±1 week) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of patients in atezolizumab-containing arms who continue treatment after radiographic disease progression; such patients will continue to undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[x] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[y] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

[z] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 7 days prior to initiation of any study treatment until the treatment discontinuation visit.

[aa] After informed consent has been obtained but prior to initiation of any study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of systemic study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of systemic study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[bb] Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The initial infusion of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details).

[dd] Bevacizumab will be administered by IV infusion at a dose of 15mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be delivered over 90 (±15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (±10) minutes. If the 60 (± 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (±15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Bevacizumab will be administered after completion of the atezolizumab infusion. Bevacizumab must be administered ≥3 days after any on-treatment biopsy, but only after adequate wound healing has been demonstrated.

[ee] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).*

Table 6 Schedule of Activities for Atezo+Bev+RTx Arm (cont.)

[ff] For details on I-SBRT planning and administration please refer to the technical radiotherapy manual.

[gg] For patients with vertebral/paraspinal metastases that are planned to be be irradiated, an MRI of this region should be considered to support the I-SBRT planning process. If an FDG-PET has been performed within 56 days of the start of the radiotherapy phase, it is strongly recommended to consider the results of the I-SBRT planning process.

Table 7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + RTx Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)

ADA = anti-drug antibody; Atezo + Bev + RTx = atezolizumab plus bevacizumab plus radiotherapy; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Note: On the basis of emerging safety or efficacy data, the number of PK and ADA samples may be reduced or sample collection may cease altogether. Additionally, collected samples may not be analyzed if not warranted. On the basis of emerging biomarker data, the number of biomarker samples may be reduced or sample collection may cease altogether.

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Appendix 20
Placeholder for Future Arm

The content of Appendix 20 Schedules of Activities for Screening has been moved to Appendix 2. Appendix 20 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 21
List of Drugs That Can Prolong QT Interval and Torsades De Pointes

This table has been adapted from Yap and Camm (2003). Please note that this list is not comprehensive.

Antiarrhythmic drugs	Type 1A (TdP reported in all)
	Quinidine (TdP reported)
	Procainamide (TdP reported)
	Disopyramide (TdP reported)
	Ajmaline (TdP reported)
	Type 1C (increase QT by prolonging QRS interval)
	Encainide
	Flecainide
	Type 3 (TdP reported in all)
	Amiodarone
	Sotalol
	d-Sotalol
	Bretylium
	Ibutilide
	Dofetilide
	Amakalant
	Semantilide
Calcium channel blockers	Prenylamine (TdP reported, withdrawn)
	Bepridil (TdP reported, withdrawn)
	Terodiline (TdP reported, withdrawn)
Psychiatric drugs	Thioridazine (TdP reported)
	Chlorpromazine (TdP reported)
	Haloperidol (TdP reported)
	Droperidol (TdP reported)
	Amitriptyline
	Nortriptyline
	Imipramine (TdP reported)
	Desipramine (TdP reported)
	Clomipramine
	Maprotiline (TdP reported)
	Doxepin (TdP reported)
Psychiatric drugs (cont.)	Lithium (TdP reported)

Appendix 21: List of Drugs That Can Prolong QT Interval and Torsades De Pointes

	Chloral hydrate
	Sertindole (TdP reported, withdrawn in the U.K.)
	Pimozide (TdP reported)
	Ziprasidone
Antihistamines	Terfenadine (TdP reported, withdrawn in the U.S.A.)
	Astemizole (TdP reported)
	Diphenhydramine (TdP reported)
	Hydroxyzine
	Ebastine
	Loratadine
	Mizolastine
Antimicrobial and antimalarial drugs	Erythromycin (TdP reported)
	Clarithromycin (TdP reported)
	Ketoconazole
	Fluconazole
	Pentamidine (TdP reported)
	Quinine
	Chloroquine (TdP reported)
	Halofantrine (TdP reported)
	Amantadine (TdP reported)
	Sparfloxacin
	Grepafloxacin (TdP reported, withdrawn in the U.K. and U.S.A.)
	Pentavalent antimonial meglumine
Serotonin agonists/antagonists	Ketanserin (TdP reported)
	Cisapride (TdP reported, withdrawn in the U.K. and U.S.A.)
Immunosuppressant	Tacrolimus (TdP reported)
Antidiuretic hormone	Vasopressin (TdP reported)
Other agents	Adenosine
	Organophosphates
	Probucol (TdP reported)
	Papaverine (TdP reported)
	Cocaine

TdP = Torsades de pointes; U.K. = United Kingdom; U.S.A. = United States of America.

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