Journal for ImmunoTherapy of Cancer

Atezolizumab and bevacizumab, with or without radiotherapy, versus docetaxel in patients with metastatic non-small cell lung cancer previously treated with a checkpoint inhibitor and chemotherapy: results from the randomized, phase Ib/II MORPHEUS-Lung study

Francois Ghiringhelli ,[1,2] Yaacov R Lawrence,[3] Enriqueta Felip,[4] Alona Zer,[5] Laurent Greillier,[6] Alastair Greystoke,[7] Nuria Pardo,[4] Nedal Al-Sakaff,[8] Hans-Joachim Helms,[8] Hen Prizant,[9] Jan Pintoffl,[8] Farah Louise Lim,[10] Sun Min Lim,[11] Byoung Chul Cho [12]

To cite: Ghiringhelli F, Lawrence YR, Felip E, *et al*. Atezolizumab and bevacizumab, with or without radiotherapy, versus docetaxel in patients with metastatic non-small cell lung cancer previously treated with a checkpoint inhibitor and chemotherapy: results from the randomized, phase Ib/II MORPHEUS-Lung study. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e011892. doi:10.1136/jitc-2025-011892

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2025-011892).

Accepted 16 June 2025

Check for updates

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to
Dr Francois Ghiringhelli; fghiringhelli@cgfl.fr

ABSTRACT

Background Options remain limited for patients requiring later lines of therapy for metastatic non-small cell lung cancer (mNSCLC) due to poor prognosis and potential toxicities. Therefore, trials of novel combinations of existing therapeutic candidates are warranted. Here, we report robust interim analysis results from the MORPHEUS-Lung study in immune checkpoint inhibitor (CPI)-exposed patients with non-squamous mNSCLC and without targetable gene mutations.

Methods MORPHEUS-Lung enrolled patients with disease progression during or following treatment with a platinum-containing regimen and a PD-L1/PD-1 immune CPI, given in combination as one line or as two separate lines of therapy, regardless of PD-L1 expression. The primary efficacy endpoint was objective response rate (ORR). Secondary efficacy endpoints included progression-free survival, duration of response, disease control rate, overall survival, and safety; exploratory endpoints included biomarkers. Patients were randomized to the atezolizumab+bevacizumab+non-ablative stereotactic body radiotherapy (SBRT), atezolizumab+bevacizumab, or docetaxel (control) arms and included in this analysis.

Results At data cut-off (August 28, 2024), 121 patients were randomized and treated: atezolizumab+bevacizumab+SBRT (n=42), atezolizumab+bevacizumab (n=40), and docetaxel (n=39). Confirmed ORR was 16.7% (6/36), 20.0% (8/40), and 12.8% (5/39) in the atezolizumab+bevacizumab+SBRT, atezolizumab+bevacizumab, and docetaxel (control) arms, respectively; one patient (2.5%) in the atezolizumab+bevacizumab arm had a complete response. Grade≥3 adverse events (AEs) occurred in 47.6% (20/42) of patients receiving atezolizumab+bevacizumab+SBRT, 45.0% (18/40) receiving atezolizumab+bevacizumab, and 64.1% (25/39) receiving docetaxel. AEs leading to discontinuation of any treatment occurred in 14.3% of patients in the atezolizumab+bevacizumab+SBRT arm, 7.5% in the atezolizumab+bevacizumab arm, and 15.4% in the docetaxel (control) arm. There were no clear correlations of response or survival benefit with PD-L1 expression or immune phenotype.

Conclusions Results from this interim analysis suggest that atezolizumab+bevacizumab, with or without SBRT,

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with metastatic non-small cell lung cancer who experienced disease progression have limited treatment options with docetaxel still considered the standard-of-care treatment for checkpoint inhibitor-exposed patients.

WHAT THIS STUDY ADDS

⇒ The MORPHEUS-Lung study allowed for the quick study of several potential treatments for these patients. Results from this analysis suggest that atezolizumab+bevacizumab, with or without stereotactic body radiotherapy, could improve efficacy outcomes compared with docetaxel with expected safety outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These combinations are potentially chemotherapy-free options for patients requiring treatment in the second line and beyond and warrant further exploration.

showed evidence of numerically improved efficacy outcomes compared with docetaxel, with a trend toward a benefit in both the primary and secondary resistance settings. Safety was consistent with the known profiles of the individual drugs, with increased toxicity observed when SBRT was added to atezolizumab+bevacizumab.

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths globally and is the most common cancer in both men and women, accounting for approximately 13% of all new cancers.[1] Non-small cell lung cancer (NSCLC) is the predominant subtype of lung cancer (approximately 85% of all cases),[2] and the two most common histologic types are adenocarcinoma (more than 50% of NSCLCs) and squamous cell carcinoma (approximately 25% of NSCLCs).[3 4] Genetic changes known to have prognostic and/or predictive significance in NSCLC include mutations in *EGFR* gene and rearrangements in the *ALK, NTRK, or ROS* genes.[5–7]

For patients with non-squamous metastatic NSCLC (mNSCLC), without oncogenic driver mutations, regardless of programmed death-ligand 1 (PD-L1) status and, standard-of-care first-line therapy includes an immune checkpoint inhibitor (CPI; single-agent or dual-agent (anti-PD1+anti-CTLA4)) with or without chemotherapy, chemotherapy alone,[8] or a combination of atezolizumab-bevacizumab-carboplatin-paclitaxel.[9] The standard-of-care first-line therapy for patients with high PD-L1 expression is single-agent CPIs such as pembrolizumab, cemiplimab, and atezolizumab.[9–11] The choice of agent for treatment of non-squamous mNSCLC in the second-line setting and beyond largely depends on the treatment a patient received in the first-line setting.[9] Pemetrexed, docetaxel, nivolumab, atezolizumab, and pembrolizumab are approved second-line agents in non-squamous NSCLC without targetable driver mutations or rearrangements.[12] Docetaxel is considered the standard-of-care treatment for immune CPI-exposed patients.[9] The overall 5-year survival rate for mNSCLC is 14.3% in the immunotherapy era vs 9% in the non-immunotherapy era[13] Given the relatively poor prognosis, limited treatment options, and potential toxicities associated with treatments for patients with CPI-exposed non-squamous mNSCLC,[14] there is a need for additional treatment options. Thus, trials of novel combinations of existing therapeutic candidates are warranted.

The MORPHEUS platform, which is composed of multiple global, open-label, randomized, phase Ib/II umbrella studies, was designed to accelerate development of novel cancer treatment combinations by identifying early efficacy and safety signals and establishing proof-of-concept data in small patient cohorts with different types of cancers.[15 16] These phase Ib/II umbrella studies feature an adaptive design that allows a single control arm to be compared with multiple experimental arms and provides the flexibility to open new or close existing treatment arms.[15–18]

Some of the novel therapeutic combinations that were studied in MORPHEUS-Lung were atezolizumab+bevacizumab+immune-modulating non-ablative stereotactic body radiotherapy (SBRT) and atezolizumab+bevacizumab. Combinations with bevacizumab were explored because bevacizumab can promote the normalization of tumor vasculature and thereby increase access of therapeutic agents.[19] In addition, bevacizumab is known to have immunomodulatory properties,[20] and it has been shown that the anti-tumor activity of atezolizumab increased when combined with bevacizumab.[21] Although radiotherapy by itself is insufficient to generate therapeutically effective anti-tumor immunity, 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.[22]

Here, we report results from an interim analysis of efficacy and safety, as well as exploratory biomarker data, of the atezolizumab+bevacizumab+SBRT, atezolizumab+bevacizumab, and docetaxel (control) arms only, from MORPHEUS-Lung study Cohort 2 (patients with non-squamous mNSCLC who had received prior immune CPI therapy).

METHODS

Study design

MORPHEUS-Lung (NCT03337698) is a phase Ib/II, open-label, multicenter, randomized, controlled, umbrella study in mNSCLC. Cohort 2 includes multiple treatment arms and consists 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) immune CPI, given in combination as one line of therapy or as two separate lines of therapy, regardless of PD-L1 expression.

Eligible patients were initially randomized to one of several treatment arms or the control arm (stage 1). Patients who experienced disease progression, loss of clinical benefit, or unacceptable toxicity during stage 1 were eligible to continue treatment with a different treatment regimen (stage 2). Enrolment of approximately 40 patients in each experimental arm occurred in a preliminary phase, potentially followed by an expansion phase whereby approximately 25 additional patients could be enrolled if clinical activity was observed during the preliminary phase.

Patients

Eligible patients in cohort 2 included those who were 18 years of age or older and had an Eastern Cooperative Oncology Group performance status of 0 or 1 with histologically or cytologically confirmed non-squamous or squamous mNSCLC. Patients with squamous histology were excluded from study arms containing bevacizumab. Eligible patients had measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and disease progression during or following

combination or sequential therapy (given as one line of therapy or as two separate lines) with a platinum-containing regimen and a PD-L1/PD-1 inhibitor. Patients could not take part in the study if they had an activating mutation in *EGFR* or an *ALK or ROS* rearrangement, prior treatment with any of the protocol-specified study treatments, or prior treatment with a T-cell co-stimulating therapy or immune CPI other than a PD-L1/PD-1 inhibitor and anti-CTLA-4 antibodies. Patients with immune CPI or biologic treatment less than 2 weeks prior to study treatment initiation, or other systemic NSCLC treatment less than 2 weeks or five half-lives of the drug (whichever was longer) prior to study treatment initiation were also excluded, as were those treated with investigational therapy less than 28 days prior to study treatment initiation.

Patients eligible for atezolizumab+bevacizumab with lesions where SBRT could be safely applied were eligible for atezolizumab+bevacizumab+SBRT. If patients who were randomized to the atezolizumab+bevacizumab+SBRT arm were not able to start treatment with SBRT due to clinical/technical reasons (eg, contraindication for SBRT, ie, detected after randomization), these patients were allowed to skip SBRT and start treatment with atezolizumab+bevacizumab and were excluded from the efficacy population.

Masking and randomization

Eligible patients were randomly assigned to a treatment arm using an interactive voice or web-based response system (IxRS). A permuted-block randomization method was used with dynamically changing randomization ratios to account for fluctuation in treatment arm numbers over the course of the study. An external company hosted the IxRS and generated the random allocation sequence. This study was an open-label study, and no blinding or masking of the treatment arms was applied.

Interventions and assessments

Atezolizumab was administered via intravenous infusion at 1200 mg on day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit. Bevacizumab was administered at 15 mg/kg intravenous on day 1 of each 21-day cycle until unacceptable toxicity or loss of clinical benefit. SBRT was administered prior to atezolizumab+bevacizumab three fractions of 8 Gy completed within 21 days (±5 days) of consent. Only photon (X-ray) beams with photon energies of at least 6 MV were allowed; charged particle beams (including electrons, protons, and heavier ions) were not allowed. Patients entered into the SBRT arm may have had any number of active lesions. Anywhere from one to five lesions, with 1 to 5 cm diameters, could be irradiated. Brain lesions, lesions abutting organs at risk, and lesions treated with radiotherapy within the last 6 months were not to be radiated. Each participating site sent a benchmark treatment plan to the Medical Monitor to ensure compliance with the protocol. The sponsor provided computer tomography datasets as a basis for the benchmark treatment plan. SBRT dose delivery was confirmed by local physics staff. Prior to treatment, each patient was discussed at quality assurance rounds or peer-reviewed by a radiation oncologist with SBRT expertise at the site, as per institutional guidelines. Docetaxel was administered at 75 mg/m^2 intravenous over 60 min on day 1 of each 21-day cycle. Irradiated lesions were included in the evaluation of objective response rate (ORR) since the primary goal was to optimize the response to immune checkpoint blockade as opposed to directly shrinking lesions. Tumor assessments were performed at baseline, every 6 weeks (±1 week) for the first 48 weeks after treatment initiation and then every 12 weeks (±2 weeks), regardless of dose delays, until radiographic disease progression according to RECIST 1.1.

Endpoints

The primary efficacy endpoint was ORR per RECIST 1.1 as assessed by the investigator. Secondary efficacy endpoints included progression-free survival (PFS), duration of response (DOR), disease control rate (DCR; all according to RECIST 1.1), and overall survival (OS). Safety was a key endpoint; exploratory endpoints included biomarkers.

Statistical analyses

Unless otherwise specified, efficacy analyses were based on the efficacy-evaluable population, defined as all patients who received at least one dose of each drug for their assigned treatment regimen. Other analyses were based on the safety-evaluable population, defined as all patients who received any amount of study treatment. Results were summarized by the treatment that patients actually received. The study was not designed to make explicit power and type I error considerations for a hypothesis test, but to obtain preliminary efficacy, safety, and PK data for atezolizumab treatment combinations in patients with mNSCLC. A sample size of approximately 40 patients per experimental arm was considered sufficient to generate preliminary efficacy and safety signals to detect clinically meaningful effects. Decisions regarding further development of a treatment combination were informed by calculating the Bayesian posterior probability of the true difference in ORR between the experimental and control arms. If the posterior probability was sufficiently high (eg, >70%) that the ORR difference was greater than a threshold value (eg, >10%), additional development could be warranted after taking into account the totality of available data for the specified treatment combination.

Best confirmed overall response (based on at least two scans) was assigned as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable as determined by the investigator according to RECIST 1.1. ORR, defined as the proportion of patients with best confirmed CR or PR, was calculated for each arm, along with 95% CIs (Clopper Pearson method). The differences in ORR between the experimental arms and the corresponding control arm were

calculated, along with 95% CIs (constructed using normal approximation to the binomial distribution). Patients with missing or no response assessments were classified as non-responders. Median PFS, OS, and DOR were estimated using the Kaplan-Meier method (95% CIs: Brookmeyer and Crowley method). OS rates at specific time points were estimated using the Kaplan-Meier method with 95% CIs calculated based on the Greenwood estimate for the variance. PFS was defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurred first. OS after randomization was defined as the time from randomization to death from any cause. DOR was defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurred first. DCR, defined as the proportion of patients with SD for ≥12 weeks, a PR, or a CR, was calculated for each arm along with 95% CIs (Clopper-Pearson exact method).

Primary and secondary resistance to immune CPIs were determined based on the patient's response to their prior initial immune CPI treatment for those treated for at least 6 weeks. Primary resistance was defined as the best overall response of PD or SD if progression occurred within 6 months from treatment initiation. Secondary resistance was defined as the best overall response of CR, PR, or SD if progression occurred after 6 months from treatment initiation.[23] In the case of concurrent treatment with chemotherapy, primary resistance was defined as progression occurring within 6 months and secondary resistance as progression occurring after 6 months, independent of overall response.[24]

Safety was assessed through summaries of adverse events (AEs), changes in laboratory test results, changes in vital signs and electrocardiograms, and exposure to study drugs. Verbatim AE terms were mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0.

Biomarker analysis

Baseline formalin-fixed paraffin-embedded tumor tissue samples were collected from all patients, preferably by biopsy performed at study entry. Where a biopsy was not deemed feasible by the investigator, archival tumor tissue was used, provided the patient had not received any immune CPI therapy since the time of the biopsy. PD-L1 expression was assessed using the Ventana PD-L1 immunohistochemistry (IHC) SP263 (Roche Diagnostics, Indianapolis, Indiana, USA) and a tumor cell (TC) score (percentage of TCs with PD-L1 membrane staining) was derived. The presence and spatial distribution of CD8 T cells were assessed using a duplex CD8-panCK IHC assay (CD8A/CD8B clone SP239; pan-cytokeratin clone AE1/AE3/PCK26). Immune statuses were derived from the assessed fraction of CD8-positive cells across the tumor area according to eight density bins (four intraepithelial bins, four intratumoral stromal bins).

RESULTS

Patient characteristics and dispositions

Enrolment in each arm occurred during the preliminary phase of enrolment only. Patients were enrolled by 36 clinical study sites across eight countries. A total of 147 patients were randomized; 45 into the atezolizumab+bevacizumab+SBRT arm (one patient with squamous disease was randomized by mistake, received three cycles of study treatment, and was excluded from the study; and two patients discontinued the study before receiving any study treatment due to withdrawal of consent or per investigator's decision), 41 into the atezolizumab+bevacizumab arm (one patient had general deterioration and was lost to follow-up before receiving any treatment), and 61 into the docetaxel (control) arm (39 who had non-squamous disease were included in the analysis). As of the data cut-off date (August 28, 2024), a total of 121 patients with non-squamous disease were enrolled and received any amount of study treatment: 42 received atezolizumab+bevacizumab+SBRT, 40 received atezolizumab+bevacizumab, and 39 received docetaxel (control). Demographics and baseline characteristics are shown in table 1. There were more patients aged 65 and older in the atezolizumab+bevacizumab+SBRT arm compared with the other two arms. Otherwise, no striking differences could be detected.

At the data cut-off date, 64.3% (27/42), 87.5% (35/40), and 94.9% (37/39) of patients in the atezolizumab+bevacizumab+SBRT arm, atezolizumab+bevacizumab arm, and docetaxel (control) arm, respectively, had discontinued from the study. Reasons for discontinuation were death, withdrawal by subject, and loss to follow-up, respectively, in 54.8%, 4.8%, and 4.8% of patients in the atezolizumab+bevacizumab+SBRT arm, 77.5%, 5.0%, and 5.0% in the atezolizumab+bevacizumab arm, and 79.5%, 15.4%, and 0.0% in the docetaxel (control) arm. Median survival follow-up was 12.5 months in the atezolizumab+bevacizumab+SBRT arm, 12.6 months in the atezolizumab+bevacizumab arm, and 9.1 months in the docetaxel (control) arm, which ensured a robust estimation of the response rate within each arm.

In the atezolizumab+bevacizumab+SBRT arm, 90.5% (38/42) of patients had at least one lesion irradiated; 78.9% (30/38), 13.2% (5/38), and 7.9% (3/38) of patients had one, two, or three lesions irradiated, respectively. The irradiated lesions were located in the lungs (50.0%), bone (15.8%), adrenal glands (15.8%), lymph nodes (15.8%), and liver (13.2%).

Efficacy

The efficacy-evaluable population (n=115) included 36 patients in the atezolizumab+bevacizumab+SBRT arm, 40 in the atezolizumab+bevacizumab arm, and 39 in the docetaxel (control) arm.

Table 1 Patient demographics and baseline characteristics

	Atezo+Bev+SBRT (n=42)	Atezo+Bev (n=40)	Doce (n=39)
Age group, n (%)			
<65 years	16 (38.1)	22 (55.0)	23 (59.0)
≥65 years	26 (61.9)	18 (45.0)	16 (41.0)
Sex, n (%)			
Male	32 (76.2)	30 (75.0)	25 (64.1)
Female	10 (23.8)	10 (25.0)	14 (35.9)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (2.5)	1 (2.6)
Not Hispanic or Latino	29 (69.0)	27 (67.5)	31 (79.5)
Not stated	12 (28.6)	12 (30.0)	5 (12.8)
Unknown	1 (2.4)	0	2 (5.1)
Race, n (%)			
Asian	13 (31.0)	5 (12.5)	9 (23.1)
White	17 (40.5)	26 (65.0)	24 (61.5)
Unknown	12 (28.6)	9 (22.5)	6 (15.4)
Baseline ECOG score, n (%)			
0	13 (31.0)	10 (25.0)	8 (20.5)
1	29 (69.0)	30 (75.0)	31 (79.5)
Metastatic sites at enrolment, n			
Median	3.0	2.5	2.0
Min-max	0–6	0–5	0–5
Metastatic sites at enrolment, n			
Non-squamous	42 (100)	40 (100)	39 (100)
Prior cancer surgery, n (%)			
Yes	6 (14.3)	13 (32.5)	9 (23.1)
No	36 (85.7)	27 (67.5)	30 (76.9)
Prior cancer radiotherapy, n (%)			
Yes	24 (57.1)	23 (57.5)	20 (51.3)
No	18 (42.9)	17 (42.5)	19 (48.7)
Smoking status, n (%)			
Present smoker	6 (14.3)	10 (25.6)	7 (17.9)
Past smoker	30 (71.4)	26 (66.7)	27 (69.2)
Never smoked	6 (14.3)	3 (7.7)	5 (12.8)
Metastatic sites at enrolment, n (%)			
Total	42	40	39
0	1 (2.4)	2 (5.0)	1 (2.6)
1	7 (16.7)	4 (10.0)	5 (12.8)
2	12 (28.6)	14 (35.0)	14 (35.9)
3	12 (28.6)	12 (30.0)	8 (20.5)
≥4	10 (23.8)	8 (20.0)	11 (28.2)
Metastatic sites at enrolment, n (%)			
n	42	40	39
Abdominal cavity	0	1 (2.5)	0
Abdominal wall	0	0	1 (2.6)

Continued

Table 1 Continued

	Atezo+Bev+SBRT (n=42)	Atezo+Bev (n=40)	Doce (n=39)
Adrenal gland	11 (26.2)	8 (20.0)	5 (12.8)
Bone	16 (38.1)	14 (35.0)	14 (35.9)
Bone marrow	1 (2.4)	0	0
Brain	10 (23.8)	3 (7.5)	11 (28.2)
Bronchus	2 (4.8)	2 (5.0)	0
Chest wall	0	1 (2.5)	1 (2.6)
Liver	10 (23.8)	11 (27.5)	9 (23.1)
Lung	22 (52.4)	23 (57.5)	23 (59.0)
Lymph node	24 (57.1)	27 (67.5)	27 (69.2)
Mediastinum	3 (7.1)	3 (7.5)	3 (7.7)
Other	9 (21.4)	5 (12.5)	8 (20.5)
Pleural cavity	3 (7.1)	4 (10.0)	2 (5.1)

Atezo, atezolizumab; Bev, bevacizumab; Doce, docetaxel; ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy.

The best confirmed ORR was 16.7% (6/36; 95% CI: 6.4 to 32.8), 20.0% (8/40; 95% CI: 9.1 to 35.7), and 12.8% (5/39; 95% CI: 4.3 to 27.4) in the atezolizumab+bevacizumab+SBRT, atezolizumab+bevacizumab, and docetaxel (control) arms, respectively (table 2). The difference in ORR rates was 3.9% (95% CI: −14.9 to 22.6) between the atezolizumab+bevacizumab+SBRT and docetaxel (control) arms and 7.2% (95% CI: −11.6 to 26.0) between the atezolizumab+bevacizumab and docetaxel (control) arms. One patient (2.5%) had a CR in the atezolizumab+bevacizumab arm. The DCR was 69.4% (25/36; 95% CI: 51.9 to 83.7) in the atezolizumab+bevacizumab+SBRT arm, 65.0% (26/40; 95% CI: 48.3 to 79.4) in the atezolizumab+bevacizumab arm, and 53.8% (21/39; 95% CI: 37.2 to 69.9) in the docetaxel (control) arm. The median DOR was not estimable (NE; 95% CI: 11.1 to NE) in the atezolizumab+bevacizumab+SBRT arm, 14.54 months (95% CI: 5.1 to 16.6) in the atezolizumab+bevacizumab arm, and 7.03 months (95% CI: 4.6 to NE) in the docetaxel (control) arm.

The number of PFS events was 26 (72.2%) in the atezolizumab+bevacizumab+SBRT arm, 39 (97.5%) in the atezolizumab+bevacizumab arm, and 32 (82.1%) in the docetaxel (control) arm. Median PFS was 7.72 months (95% CI: 4.4 to 11.4) in the atezolizumab+bevacizumab+SBRT arm (HR, 0.53; 95% CI: 0.3 to 0.9 vs control), 6.95 months (95% CI: 4.4 to 8.3) in the atezolizumab+bevacizumab arm (HR, 0.74; 95% CI: 0.5 to 1.2 vs control),

Table 2 Best confirmed overall response rates by investigator

	Atezo+Bev+SBRT (n=36)	Atezo+Bev (n=40)	Doce (n=39)
Responders, n (%) (95% CI)	6 (16.7) (6.37 to 32.81)	8 (20.0) (9.05 to 35.65)	5 (12.8) (4.30 to 27.43)
Complete response, n (%) (95% CI)	0 (0.00 to 9.74)	1 (2.5) (0.06 to 13.16)	0 (0.00 to 9.03)
Partial response, n (%) (95% CI)	6 (16.7) (6.37 to 32.81)	7 (17.5) (7.34 to 32.78)	5 (12.8) (4.30 to 27.43)
Stable disease, n (%) (95% CI)	22 (61.1) (43.46 to 76.86)	20 (50.0) (33.80 to 66.20)	21 (53.8) (37.18 to 69.91)
Progressive disease, n (%) (95% CI)	8 (22.2) (10.12 to 39.15)	7 (17.5) (7.34 to 32.78)	9 (23.1) (11.13 to 39.33)
Not evaluable, n (%)	0	2 (5.0)	1 (2.6)
Missing, n (%)	0	3 (7.5)	3 (7.7)
Disease control rate, n (%) (95% CI)	25 (69.4) (51.89 to 83.65)	26 (65.0) (48.32 to 79.37)	21 (53.8) (37.18 to 69.91)

Atezo, atezolizumab; Bev, bevacizumab; Doce, docetaxel; SBRT, stereotactic body radiotherapy.

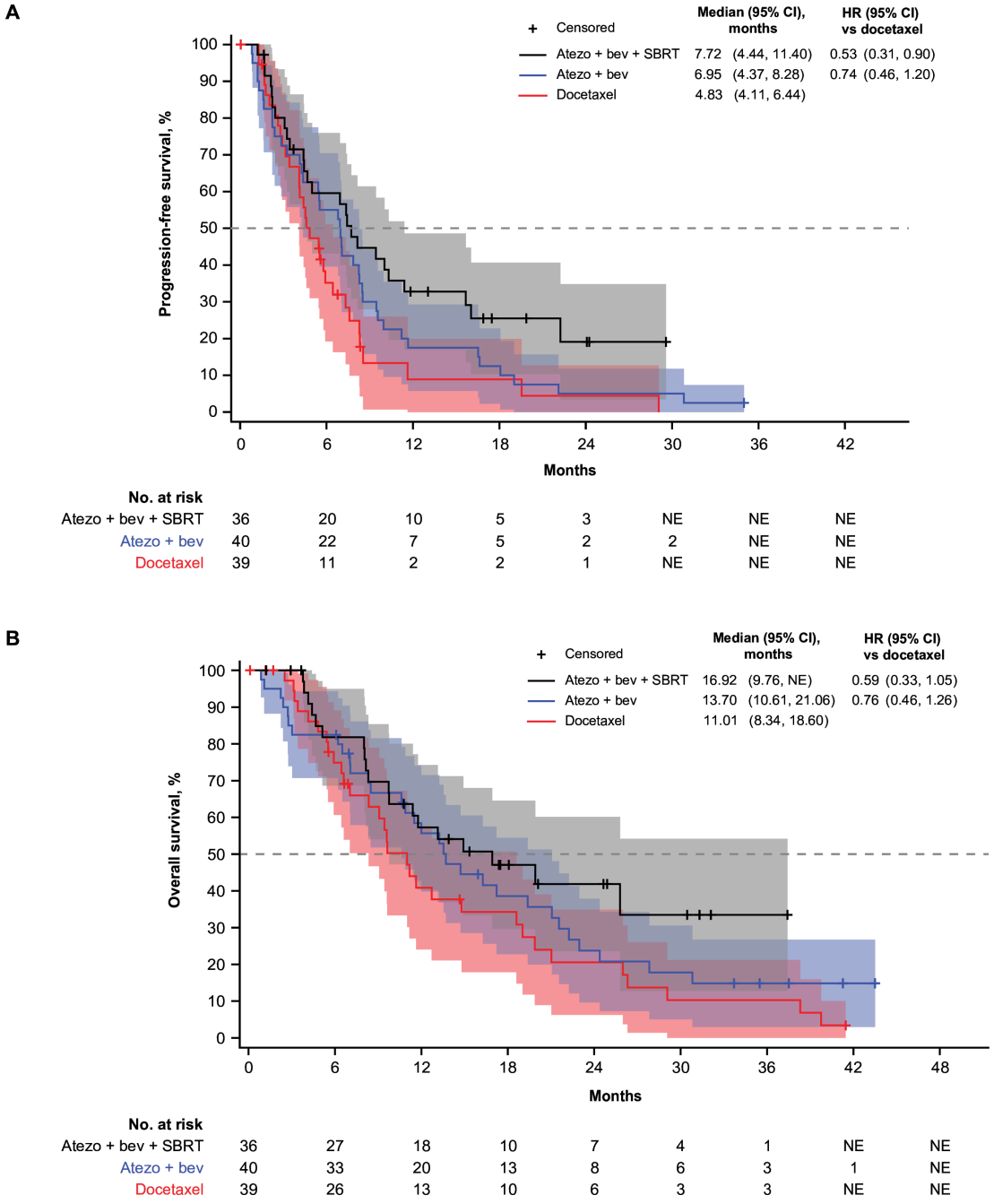


Figure 1 Progression-free survival (A) and overall survival (B). Atezo, atezolizumab; bev, bevacizumab; doce, docetaxel; NE, not estimable; SBRT, stereotactic body radiotherapy.

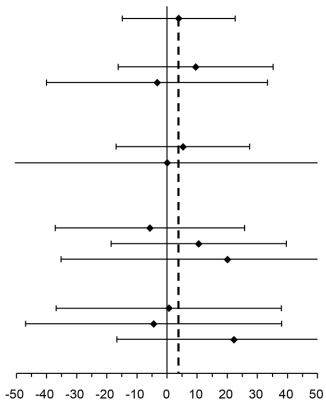
and 4.83 months (95% CI: 4.1 to 6.4) in the docetaxel (control) arm (figure 1A).

For OS, the event numbers were 19 (52.8%) in the atezolizumab+bevacizumab+SBRT arm, 31 (77.5%) in the atezolizumab+bevacizumab arm, and 31 (79.5%) in the docetaxel (control) arm. Median OS was 16.92 months (95% CI: 9.76 to NE) in the atezolizumab+bevacizumab+SBRT arm (HR, 0.59; 95% CI: 0.33 to 1.05 vs control), 13.70 months (95% CI: 10.6 to 21.1) in the atezolizumab+bevacizumab arm (HR, 0.76; 95% CI: 0.5 to 1.3 vs control), and 11.01 months (95% CI: 8.34 to 18.60) in the docetaxel (control) arm (figure 1B). Efficacy outcomes (ORR, PFS, OS) appeared to be mostly consistent across key clinical subgroups (figures 2 and 3).

Trends toward improved efficacy were observed in the atezolizumab+bevacizumab+SBRT and atezolizumab+bevacizumab arms versus docetaxel in the subgroups of patients with primary and secondary resistance to immune CPIs (except for ORR with atezolizumab+bevacizumab+ SBRT in the subgroup of patients with primary resistance to immune CPIs; figure 2). However, these results should be interpreted with caution, given the small sample sizes and wide and overlapping CIs.

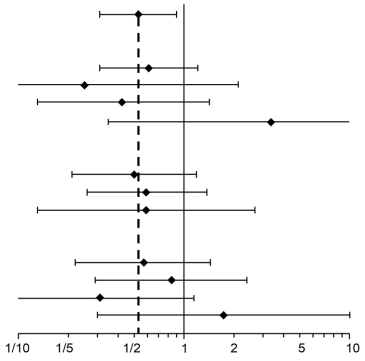
A

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Responder n	Doce (N=39) Response (%)	Atezo+Bev+SBRT (N=36) n	Atezo+Bev+SBRT (N=36) Responder n	Atezo+Bev+SBRT (N=36) Response (%)	Difference in Rates	95% CI
All Patients	75	39	5	12.8	36	6	16.7	3.85	(-14.90, 22.59)
Baseline SP263 TC Binary Category 1									
<1%	42	21	2	9.5	21	4	19.0	9.52	(-16.21, 35.25)
≥1%	27	15	3	20.0	12	2	16.7	-3.33	(-40.06, 33.40)
NA	6	3	0	NE	3	0	NE		
Baseline SP263 TC Binary Category 2									
<50%	53	28	3	10.7	25	4	16.0	5.29	(-16.88, 27.45)
≥50%	16	8	2	25.0	8	2	25.0	0	(-54.93, 54.93)
NA	6	3	0	NE	3	0	NE		
CPI Resistance									
Primary Resistance	34	20	4	20.0	14	2	14.3	-5.71	(-37.15, 25.72)
Secondary Resistance	31	14	1	7.1	17	3	17.6	10.5	(-18.60, 39.61)
NA	10	5	0	NE	5	1	20.0	20	(-35.06, 75.06)
Immune Status CD8 Category									
Inflamed	27	11	2	18.2	16	3	18.8	0.57	(-36.86, 37.99)
Excluded	23	16	3	18.8	7	1	14.3	-4.46	(-46.95, 38.02)
Desert	17	8	0	NE	9	2	22.2	22.22	(-16.74, 61.19)
Unknown	8	4	0	NE	4	0	NE		



B

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Median (months)	Atezo+Bev+SBRT (N=36) n	Atezo+Bev+SBRT (N=36) Median (months)	Hazard Ratio	95% Wald CI
All Patients	75	39	4.8	36	7.7	0.53	(0.31, 0.90)
Baseline SP263 TC Category							
<1%	42	21	4.8	21	7.4	0.61	(0.31, 1.21)
1-49%	11	7	3.5	4	NE	0.25	(0.03, 2.12)
≥50%	16	8	6.4	8	15.7	0.42	(0.13, 1.42)
NA	6	3	8.3	3	4.4	3.35	(0.35, 32.39)
CPI Resistance							
Primary Resistance	34	20	4.7	14	6.0	0.50	(0.21, 1.19)
Secondary Resistance	31	14	5.5	17	8.1	0.59	(0.26, 1.37)
NA	10	5	4.7	5	7.0	0.59	(0.13, 2.68)
Immune Status CD8 Category							
Inflamed	27	11	5.0	16	10.3	0.57	(0.22, 1.44)
Excluded	23	16	5.2	7	3.4	0.84	(0.29, 2.40)
Desert	17	8	3.2	9	10.0	0.31	(0.09, 1.15)
Unknown	8	4	6.2	4	5.9	1.73	(0.30, 10.02)



C

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Median (months)	Atezo+Bev+SBRT (N=36) n	Atezo+Bev+SBRT (N=36) Median (months)	Hazard Ratio	95% Wald CI
All Patients	75	39	11.0	36	16.9	0.59	(0.33, 1.05)
Baseline SP263 TC Category							
<1%	42	21	10.4	21	11.8	0.63	(0.30, 1.34)
1-49%	11	7	7.0	4	NE	0.17	(0.02, 1.54)
≥50%	16	8	11.6	8	22.9	0.55	(0.16, 1.94)
NA	6	3	26.5	3	16.9	1.62	(0.14, 18.31)
CPI Resistance							
Primary Resistance	34	20	11.0	14	14.8	0.73	(0.30, 1.76)
Secondary Resistance	31	14	18.6	17	16.9	0.55	(0.22, 1.39)
NA	10	5	8.0	5	13.1	0.64	(0.13, 3.24)
Immune Status CD8 Category							
Inflamed	27	11	11.6	16	25.8	0.52	(0.18, 1.49)
Excluded	23	16	9.4	7	8.0	1.31	(0.50, 3.47)
Desert	17	8	11.2	9	19.9	0.20	(0.04, 1.02)
Unknown	8	4	14.8	4	14.3	1.15	(0.19, 6.95)

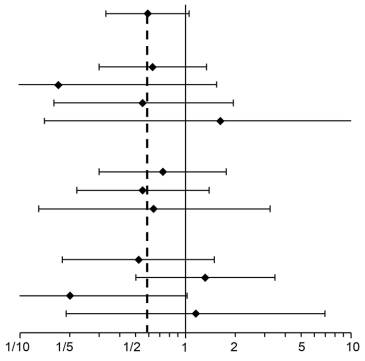


Figure 2 Objective response rate (A), progression-free survival (B) and overall survival (C) based on response to previous checkpoint inhibitors in the atezolizumab+bevacizumab+SBRT arm. Atezo, atezolizumab; bev, bevacizumab; CPI, checkpoint inhibitor; NA, not applicable; NE, non estimable; SBRT, stereotactic body radiotherapy; TC, tumor cell.

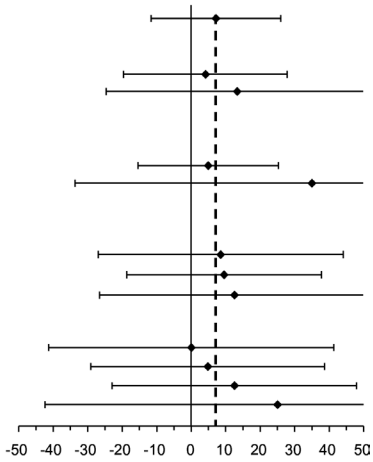
Safety

The safety-evaluable population (n=121) included 42 patients in the atezolizumab+bevacizumab+SBRT arm, 40 in the atezolizumab+bevacizumab arm, and 39 in the docetaxel (control) arm. An overall safety summary is presented in table 3.

The most frequent AEs were asthenia (40.5%, 12.5%, and 38.5% of patients), followed by lymphopenia (23.8%, 12.5%, and 0% of patients), and rash (16.7%, 5.0%, and 7.7% of patients) in the atezolizumab+bevacizumab+SBRT, atezolizumab+bevacizumab, and docetaxel arms, respectively (online supplemental table 1). Most of these AEs were grade 1 or 2. Grade ≥3 AEs occurred in 47.6% of patients in the atezolizumab+bevacizumab+SBRT arm, 45.0% in the atezolizumab+bevacizumab arm, and 64.1% in the docetaxel (control) arm. AEs leading to discontinuation of any treatment occurred in 14.3% of patients in the atezolizumab+bevacizumab+SBRT arm, 7.5% in the atezolizumab+bevacizumab arm, and 15.4% in the docetaxel (control) arm. Five grade 5 AEs were reported

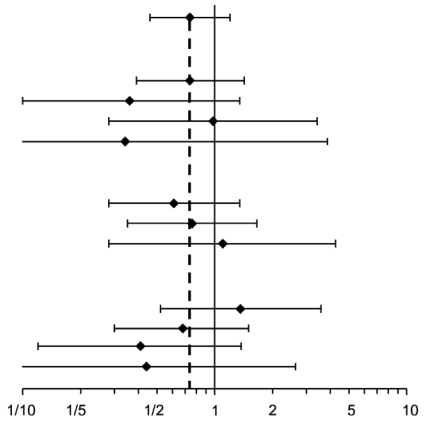
A

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Responder n	Doce (N=39) Response (%)	Atezo+Bev (N=40) n	Atezo+Bev (N=40) Responder n	Atezo+Bev (N=40) Response (%)	Difference in Rates	95% CI
All Patients	79	39	5	12.8	40	8	20.0	7.18	(-11.59, 25.95)
Baseline SP263 TC Binary Category 1									
<1%	43	21	2	9.5	22	3	13.6	4.11	(-19.60, 27.83)
≥1%	30	15	3	20.0	15	5	33.3	13.33	(-24.62, 51.29)
NA	6	3	0	NE	3	0	NE		
Baseline SP263 TC Binary Category 2									
<50%	60	28	3	10.7	32	5	15.6	4.91	(-15.45, 25.27)
≥50%	13	8	2	25.0	5	3	60.0	35.00	(-33.64, 100.00)
NA	6	3	0	NE	3	0	NE		
CPI Resistance									
Primary Resistance	34	20	4	20.0	14	4	28.6	8.57	(-26.95, 44.09)
Secondary Resistance	32	14	1	7.1	18	3	16.7	9.52	(-18.70, 37.75)
NA	13	5	0	NE	8	1	12.5	12.50	(-26.67, 51.67)
Immune Status CD8 Category									
Inflamed	22	11	2	18.2	11	2	18.2	0.00	(-41.32, 41.32)
Excluded	33	16	3	18.8	17	4	23.5	4.78	(-29.08, 38.64)
Desert	16	8	0	NE	8	1	12.5	12.50	(-22.92, 47.92)
Unknown	8	4	0	NE	4	1	25.0	25.00	(-42.43, 92.43)



B

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Median (months)	Atezo+Bev (N=40) n	Atezo+Bev (N=40) Median (months)	Hazard Ratio	95% Wald CI
All Patients	79	39	4.8	40	6.9	0.74	(0.46, 1.20)
Baseline SP263 TC Category							
<1%	43	21	4.8	22	6.2	0.74	(0.39, 1.42)
1-49%	17	7	3.5	10	6.9	0.36	(0.10, 1.35)
≥50%	13	8	6.4	5	7.0	0.98	(0.28, 3.42)
NA	6	3	8.3	3	8.5	0.34	(0.03, 3.85)
CPI Resistance							
Primary Resistance	34	20	4.7	14	7.7	0.61	(0.28, 1.35)
Secondary Resistance	32	14	5.5	18	6.2	0.76	(0.35, 1.66)
NA	13	5	4.7	8	8.2	1.10	(0.28, 4.25)
Immune Status CD8 Category							
Inflamed	22	11	5.0	11	6.9	1.36	(0.52, 3.57)
Excluded	33	16	5.2	17	5.5	0.68	(0.30, 1.50)
Desert	16	8	3.2	8	7.6	0.41	(0.12, 1.37)
Unknown	8	4	6.2	4	7.0	0.44	(0.07, 2.65)



C

Baseline Risk Factors	Total n	Doce (N=39) n	Doce (N=39) Median (months)	Atezo+Bev (N=40) n	Atezo+Bev (N=40) Median (months)	Hazard Ratio	95% Wald CI
All Patients	79	39	11.0	40	13.7	0.76	(0.46, 1.26)
Baseline SP263 TC Category							
<1%	43	21	10.4	22	13.2	0.81	(0.41, 1.59)
1-49%	17	7	7.0	10	10.9	0.34	(0.10, 1.19)
≥50%	13	8	11.6	5	21.1	0.70	(0.18, 2.64)
NA	6	3	26.5	3	23.0	2.33	(0.24, 22.78)
CPI Resistance							
Primary Resistance	34	20	11.0	14	11.9	0.91	(0.42, 1.97)
Secondary Resistance	32	14	18.6	18	16.3	0.74	(0.32, 1.69)
NA	10	5	8.0	8	13.4	0.75	(0.21, 2.64)
Immune Status CD8 Category							
Inflamed	22	11	11.6	11	13.5	0.88	(0.34, 2.23)
Excluded	33	16	9.4	17	12.0	0.81	(0.37, 1.77)
Desert	16	8	11.2	8	17.2	0.48	(0.13, 1.73)
Unknown	8	4	14.8	4	23.0	1.06	(0.17, 6.47)

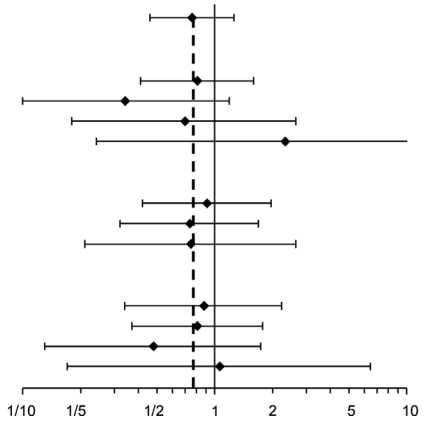


Figure 3 Objective response rate (A), progression-free survival (B) and overall survival (C) based on response to previous checkpoint inhibitors in the atezolizumab+bevacizumab arm. Atezo, atezolizumab; bev, bevacizumab; doce, docetaxel; NA, not applicable; NE, not estimable; TC, tumor cell.

in total, four of which occurred in the atezolizumab+bevacizumab+SBRT arm (acute cerebral infarction during the SBRT, suicide, death due to an unknown reason, and intestinal obstruction occurring during systemic therapy). Acute cerebral infarction was considered by investigators to be unrelated to atezolizumab and bevacizumab; suicide, death due to an unknown reason, and intestinal obstruction occurring during systemic therapy were

Table 3 Safety summary

	Atezo+Bev+SBRT (n=42)	Atezo+Bev (n=40)	Doce (n=39)
Patients with ≥1 AE, n (%)	41 (97.6)	38 (95.0)	39 (100)
AEs, n	493	423	321
Deaths, n (%)	20 (47.6)	22 (55.0)	23 (59.0)
Patients withdrawn from stage due to an AE, n (%)	3 (7.1)	3 (7.5)	5 (12.8)
Patients with ≥1, n (%)			
AE with fatal outcome	4 (9.5)	0	1 (2.6)
Serious AE	16 (38.1)	13 (32.5)	13 (33.3)
Serious AE leading to withdrawal from any treatment	5 (11.9)	2 (5.0)	2 (5.1)
Serious AE leading to dose modification/interruption	7 (16.7)	4 (10.0)	5 (12.8)
Related serious AE	3 (7.1)	5 (12.5)	9 (23.1)
AE leading to withdrawal from any treatment	6 (14.3)	3 (7.5)	6 (15.4)
AE leading to dose modification/interruption	21 (50.0)	15 (37.5)	17 (43.6)
Related AE	30 (71.4)	34 (85.0)	38 (97.4)
Related AE leading to withdrawal from any treatment	2 (4.8)	3 (7.5)	5 (12.8)
Related AE leading to dose modification/interruption	14 (33.3)	11 (27.5)	13 (33.3)
Grade 3–5 AE	20 (47.6)	18 (45.0)	25 (64.1)
Worst grade: 5	4 (9.5)	0	1 (2.6)
Worst grade: 4	1 (2.6)	0	4 (10.3)
Worst grade: 3	15 (35.7)	18 (45.0)	20 (51.3)

AE, adverse event; Atezo, atezolizumab; Bev, bevacizumab; Doce, docetaxel; SBRT, stereotactic body radiotherapy.

considered by investigators to be unrelated to study treatment. One fatal AE (pneumonia considered by the investigator as related to docetaxel) occurred in the docetaxel (control) arm. Seven of 42 patients (16.7%) experienced at least one AE related to SBRT during the SBRT phase, including one patient with grade 3 bronchial fistula.

Biomarkers

Analysis of tumor biomarkers by IHC and clinical outcome is shown in figure 4. There are no clear correlations of response or survival benefit with PD-L1 expression or immune phenotype; however, patients with PD-L1-negative and immune desert tumors also seem to derive a benefit from atezolizumab+bevacizumab with or without SBRT treatment (figures 2 and 3). Interestingly, the trend of benefit from atezolizumab+bevacizumab with or without SBRT treatment is observed among patients with primary resistance as well as with secondary resistance to their prior initial immune CPI treatment (figures 2 and 3). The small patient numbers in the biomarker subsets and the wide CIs limit the interpretation of biomarkers.

DISCUSSION

The MORPHEUS platform, which comprises multiple global, open-label, randomized, phase Ib/II umbrella studies, was designed to accelerate development of novel cancer treatment combinations. Here, the chemotherapy-free regimens of atezolizumab+bevacizumab+SBRT and atezolizumab+bevacizumab were compared with docetaxel, in patients with non-squamous mNSCLC and without targetable gene mutations who had experienced disease progression on or after treatment with a platinum-containing regimen and a PD-L1/PD-1 immune CPI. Across clinical subgroups, the atezolizumab-containing and bevacizumab-containing arms showed evidence of improved efficacy compared with docetaxel (control), with the docetaxel arm performing as expected based on past studies.[25–30] Additionally, the atezolizumab and bevacizumab combinations showed acceptable safety profiles with no new safety signals observed.

The ability to maximize clinical benefit from immune CPI for patients is limited by resistance to immunotherapy, whether it be primary resistance where tumors do not respond to initial immune CPI treatment or secondary resistance where patients have disease recurrence or progression after achieving benefit with immune CPIs.[31] The potential efficacy benefit seen in MORPHEUS-Lung appears in both the primary and the secondary resistance settings, consistent with the hypothesis that combining treatment modalities can result in more robust efficacy.

Overall, identifying new treatments for pretreated mNSCLC remains a challenge.[25–30 32] The combination of PD-1/PD-L1 and VEGF inhibition seems to be one of the more promising approaches to overcome immune CPI resistance as VEGF inhibitors modulate the tumor microenvironment, normalizing its vasculature and modulating

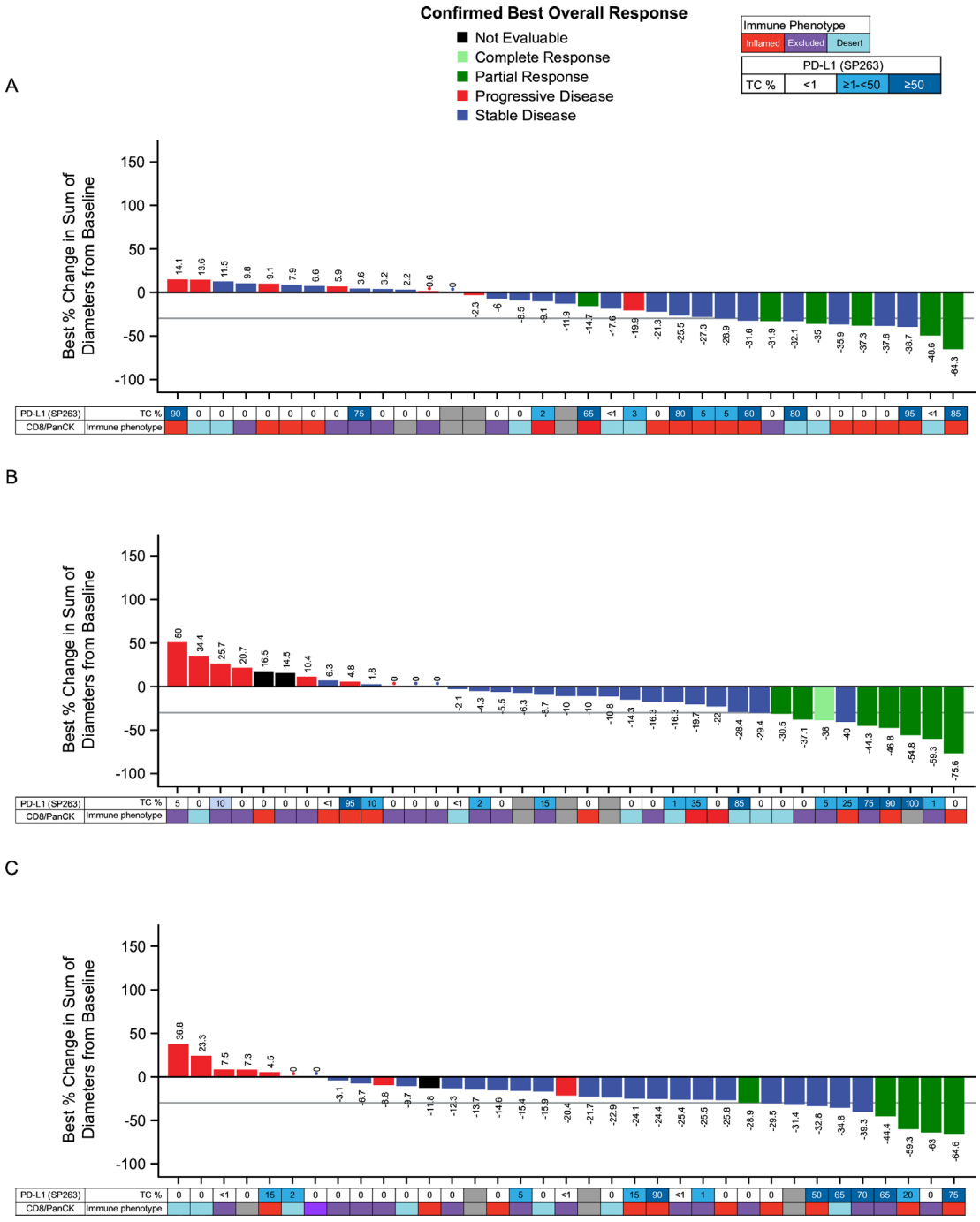


Figure 4 Confirmed best overall response according to biomarkers in the atezolizumab+bevacizumab+SBRT arm (A), atezolizumab+bevacizumab arm (B), and docetaxel arm (C). PD-L1, programmed death-ligand 1; SBRT, stereotactic body radiotherapy; TC, tumor cell.

an immunoreactive niche favoring immune ICI activity. VEGF may also contribute to the immune suppression of the tumor microenvironment, increase myeloid-derived suppressor cells, and stimulate the production of immunosuppressive cells.[33] Our study underscores the importance of this mechanism of action in immune CPI-exposed patients with NSCLC.

SBRT modifies PD-L1 expression, activates the immune system, and can thus enhance ICI effectiveness. Laboratory studies have demonstrated that radiotherapy can enhance the effectiveness of immunotherapy by increasing the immunogenicity of the tumor.[34] While the combination of PD-1/PD-L1 inhibitors has demonstrated improved efficacy in advanced and early NSCLC in several phase I and II trials,[30 32 35 36] MORPHEUS is the first study that investigated the effect of SBRT in combination with ICI and a VEGF inhibitor in patients with NSCLC who progressed on or after treatment with platinum continuing chemotherapy and an immune CPI inhibitor. However, the addition of SBRT appears

to increase toxicity, in line with previous studies of SBRT combined with immunotherapy.[37 38]

Taken together, the above results demonstrate the importance of continuing to explore biomarkers to improve patient outcomes in mNSCLC. In MORPHEUS-Lung, there was no clear correlation between response and PD-L1 expression or immune phenotype. However, it is important to note that patients with PD-L1-negative and immune desert tumors also derived benefit from atezolizumab+bevacizumab with or without SBRT treatment.

The study design of MORPHEUS-Lung allowed for the quick simultaneous evaluation of multiple treatment combinations in a global randomized setting, which provides an advantage compared with conducting multiple controlled standalone phase Ib/II studies. However, the study comes with several limitations:

1. Small number of patients in each arm can make the interpretation of the results challenging.
2. MORPHEUS-Lung was set up as a signal-seeking study without formal hypothesis testing and alpha control.
3. Study was not designed to compare atezolizumab+bevacizumab+SBRT with atezolizumab+bevacizumab.
4. Enrolment was independent of prior response to immune CPI, which may have led to an imbalance between the arms in regard to this characteristic.
5. Enrolment was not concurrent in all three arms resulting in different follow-up times in each arm, which could potentially impact interpretation of early OS results.
6. Lack of standardization regarding which lesions were irradiated in the atezolizumab+bevacizumab+SBRT arm, and not all patients were able to receive SBRT treatment.

Despite these limitations, a key strength of these interim results is that they can be considered mature due to the long follow-up times and overall high number of efficacy events.

CONCLUSIONS

Results from this robust interim analysis of patients with non-squamous mNSCLC and prior immune CPI treatment suggest that atezolizumab+bevacizumab, with or without SBRT, might improve efficacy outcomes compared with docetaxel, in both the primary and secondary resistance settings. The addition of SBRT appeared to augment the activity of atezolizumab+bevacizumab. The benefit trends in both arms were irrespective of PD-L1 or immune status. Safety was consistent with the known profiles of the individual drugs. The promising results for atezolizumab+bevacizumab, with or without SBRT, including improved survival, represent a potential chemotherapy-free treatment option for patients with non-squamous mNSCLC in the challenging second-line and beyond, immune CPI-exposed treatment setting, warranting further exploration.

Author affiliations
[1]Université Bourgogne Europe, Dijon, France
[2]Early Clinical Trial Unit, Centre Georges-Francois Leclerc, Dijon, France
[3]The Benjamin Davidai Department of Radiation Oncology, Sheba Medical Center, Tel HaShomer, Israel
[4]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
[5]Institute of Oncology, Rambam Health Campus, Haifa, Israel
[6]APHM, INSERM, CNRS, CRCM, Hôpital Nord, Multidisciplinary Oncology and Therapeutic Innovations, Aix Marseille Université, Marseille, France
[7]Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University Centre for Cancer, Newcastle upon Tyne, UK
[8]F Hoffmann-La Roche Ltd, Basel, Switzerland
[9]Genentech Inc, South San Francisco, California, USA
[10]Queen Mary University of London, London, UK
[11]Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of)
[12]Yonsei Cancer Center, Yonsei University College of Medicine, Seodaemun-gu, Seoul, Korea (the Republic of)

Acknowledgements We thank all of the patients who participated in the trial, their families, and the investigators, clinicians, and research staff at the 36 clinical study sites across eight countries. We thank Dr Alexandra Giraldo (Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain) for significant contribution to the design of the atezolizumab+bevacizumab+SBRT arm, and Alejandro Seoane Ramallo, MSc, (Physics Department, Vall d'Hebron University Hospital, Barcelona, Spain) for continuous review of the radiation plans. Support for third-party writing assistance for this manuscript, furnished by Chantel Swart, PhD, of Nucleus Global, an Inizio Company, was provided by F. Hoffmann-La Roche.

Contributors Conceptualization: BCC, HP, JP, NA-S and YRL. Methodology: BCC, NA-S and YRL. Validation: NA-S. Formal analysis: BCC, H-JH, HP and YRL. Investigation: AG, BCC, EF, FG, LG, JP and NP. Resources: AG, BCC, EF, LG, SML, YRL and AZ. Data curation: BCC and NA-S, Writing– original draft: BCC, HP and JP. Writing–review and editing: AG, BCC, EF, FG, FLL, LG, H-JH, HP, NA-S, NP, JP, SML, YRL and AZ. Supervision: YRL. Project administration: NA-S. Guarantor: FG.

Funding This study was funded by F. Hoffmann-La Roche.

Competing interests AG received a research funding grant from AstraZeneca; consulting fees from F. Hoffmann-La Roche, Bristol Myers Squibb, Takeda, Pfizer, AstraZeneca, Amgen, Merck Serano, Boehringer Ingelheim, Novartis, Janssen, Eli Lilly, and Sanofi; received payment or honoraria from F. Hoffmann-La Roche, Bristol Myers Squibb, Takenda, Pfizer, AstraZeneca, Amgen, Merck Serono, Boehringer Ingelheim, Novartis, Janssen, Eli Lilly, and Sanofi; travel support from F. Hoffmann-La Roche and Takeda. AZ received consulting fees from Merck Sharp and Dohme, Beigene, AstraZeneca, AbbVie, F. Hoffmann-La Roche, and Beyond Cancer; payment or honoraria from AstraZeneca, F. Hoffmann-La Roche, AbbVie, Johnson & Johnson, and Pfizer; travel support from F. Hoffmann-La Roche; and participated on a data safety monitoring board or advisory board for Beyond Cancer and Merck Sharp and Dohme. BCC received grants or contracts from GIInnovation, AstraZeneca, Champions Oncology, CJ Bioscience, Cyrus, Janssen, MSD, Dong-A ST, Yuhan, ImmuneOncia, Therapex, J INTS Bio, and Vertical Bio AG; royalties or licenses from Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio; consulting fees from BeiGene, Novartis, AstraZeneca, Boehringer-Ingelheim, F. Hoffmann-La Roche, Bristol Meyers Squibb, CJ, Cyrus Therapeutics, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, Merck Sharp and Dohme, Gilead, Amgen, Daiichi Sankyo, Regeneron, Sanofi, AnHeart Therapeutics, Seagen, Harpoon Therapeutics, GSK, and ArriVent; received payment or honoraria from ASCO, AstraZeneca, Guardant, F. Hoffmann-La Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, Merck Sharp and Dohme, The Chinese Thoracic Oncology Society, Pfizer and Zailab; participated on a scientific advisory board for KANAPH Therapeutic, Bridgebio therapeutics, Cyrus Therapeutics, Guardant Health, J INTS Bio and Therapex Co., is a member of the board of directors for J INTS Bio; owns stocks of TheraCanVac, Gencurix, Bridgebio Therapeutics, KANAPH Therapeutic Inc, Cyrus Therapeutics, Interpark Bio Convergence Corp, and J INTS BIO; and is a founder of DAAN Biotherapeutics. EF received consulting fees from AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, F. Hoffmann-La Roche, Gilead, GlaxoSmithKline, Iteos Therapeutics, Janssen, Johnson & Johnson, Merck Sharp and Dohme, Novartis, Pierre Fabre, Pfizer, Regeneron, and Turning Point; received honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffmann-La Roche, Genentech,

Gilead, Janssen, Johnson & Johnson, Medical Trends, Medscape, Merck Serono, Merck Sharp and Dohme, Novartis, Peervoice, Pfizer, and Regeneron; received travel support from AstraZeneca, Janssen, and F. Hoffmann-La Roche; and is an independent member of the board for Grifols. FG has nothing to declare. FLL received payments or honoraria from Lung Cancer Expert Forum and travel support from F. Hoffmann-La Roche. LG received grants or contracts to their institution from Bristol Myers Squibb, Merck Sharp and Dohme, Takeda, Pfizer, F. Hoffmann-La Roche, Amgen, Sanofi, Janssen, Eli Lilly, and Novartis; payments or honoraria from Bristol Myers Squibb, Merck Sharp and Dohme, Takeda, Pfizer, F. Hoffmann-La Roche, Amgen, Sanofi, Janssen, Eli Lilly, and Novartis; travel support from Pfizer, Merck Sharp and Dohme, AstraZeneca, Takeda, and Amgen; and participated on a data safety monitoring board or advisory board for Inhatarget Therapeutics. NP received payment or honoraria from F. Hoffmann-La Roche and Takeda, and travel support from Merck Sharp and Dohme, F. Hoffmann-La Roche, Takeda, and Pfizer. SML has nothing to declare. YRL received consulting fees from F. Hoffmann-La Roche for this project and a payment to institution from Zola Therapeutics; and owns stock in Protean Biodiagnostics. NA-S, H-JH, HP and JP are employees of F. Hoffmann-La Roche or Genentech and own stock.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was conducted in conformance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was reviewed and approved by the institutional review board or ethics committee at each study site. All amendments affecting trial recruitment and conduct were approved (SI number: 18.00310.201803-MS16; National number: 2017-001267-21; Internal reference: BO39610). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Qualified researchers may request access to individual patient-level data through the clinical study data request platform: https://vivli.org/. Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see: https://www.roche.com/research_and_development/who_we_are_how_we_work/clini cal_trials/our_commitment_to_data_sharing.htm.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Francois Ghiringhelli http://orcid.org/0000-0002-5465-8305
Byoung Chul Cho http://orcid.org/0000-0002-5562-270X

REFERENCES

1 Jemal A, Bray F, Center MM, *et al*. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
2 Howlader N, Noone AM, Krapcho M, eds. *SEER cancer statistics review, 1975-2013*. National Cancer Institute. Bethesda, 2016. Available: https://seer.cancer.gov/archive/csr/1975_2013
3 Langer CJ, Besse B, Gualberto A, *et al*. The evolving role of histology in the management of advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:5311–20.
4 Travis WD, Brambilla E, Noguchi M, *et al*. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–85.
5 Marks JL, Broderick S, Zhou Q, *et al*. Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. *J Thorac Oncol* 2008;3:111–6.
6 Wang Z, Yang H, Luo S, *et al*. Anaplastic lymphoma kinase gene rearrangement predicts better prognosis in NSCLC patients: A meta-analysis. *Lung Cancer (Auckl)* 2017;112:1–9.
7 Zhang H, Shan G, Cai B, *et al*. Clinicopathological and prognostic implications of ALK rearrangement in patients with completely surgically resected lung adenocarcinoma. *Thorac Cancer* 2021;12:3011–8.
8 Tian W, Niu L, Shi Y, *et al*. First-line treatments for advanced non-squamous non-small cell lung cancer with immune checkpoint inhibitors plus chemotherapy: a systematic review, network meta-analysis, and cost-effectiveness analysis. *Ther Adv Med Oncol* 2024;16:17588359241255613.
9 Hendriks LE, Kerr KM, Menis J, *et al*. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:339–57.
10 Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823–33.
11 Hellmann MD, Paz-Ares L, Bernabe Caro R, *et al*. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019;381:2020–31.
12 Hendriks LE, Kerr KM, Menis J, *et al*. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:358–76.
13 Wang Y, Kondrat K, Adhikari J, *et al*. Survival trends among patients with metastatic non–small cell lung cancer before and after the approval of immunotherapy in the United States: A Surveillance, Epidemiology, and End Results database–based study. *Cancer* 2025;131:e35476.
14 Insa A, Martín-Martorell P, Di Liello R, *et al*. Which treatment after first line therapy in NSCLC patients without genetic alterations in the era of immunotherapy? *Crit Rev Oncol Hematol* 2022;169:103538.
15 Chau I, Haag GM, Rahma OE, *et al*. MORPHEUS: A phase Ib/II umbrella study platform evaluating the safety and efficacy of multiple cancer immunotherapy (CIT)-based combinations in different tumour types. *Ann Oncol* 2018;29:viii439–40.
16 Johnson ML, Solomon BJ, Awad MM, *et al*. MORPHEUS: A phase Ib/II multi-trial platform evaluating the safety and efficacy of cancer immunotherapy (CIT)-based combinations in patients (pts) with non-small cell lung cancer (NSCLC). *J Clin Oncol* 2018;36:TPS9105.
17 Drakaki A, Powles T, Bamias A, *et al*. Atezolizumab plus magrolimab, niraparib, or tocilizumab versus atezolizumab monotherapy in platinum-refractory metastatic urothelial carcinoma: A phase Ib/II open-label, multicenter, randomized umbrella study (MORPHEUS Urothelial Carcinoma). *Clin Cancer Res* 2023;29:4373–84.
18 Ko AH, Kim K-P, Siveke JT, *et al*. Atezolizumab plus PEGPH20 versus chemotherapy in advanced pancreatic ductal adenocarcinoma and gastric cancer: MORPHEUS phase Ib/II umbrella randomized study platform. *Oncologist* 2023;28:553–e472.
19 Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 2001;7:987–9.
20 Rahma OE, Hodi FS. The intersection between tumor angiogenesis and immune suppression. *Clin Cancer Res* 2019;25:5449–57.
21 Wallin JJ, Bendell JC, Funke R, *et al*. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016;7:12624.
22 Vanpouille-Box C, Pilones KA, Wennerberg E, *et al*. In situ vaccination by radiotherapy to improve responses to anti-CTLA-4 treatment. *Vaccine (Auckl)* 2015;33:7415–22.
23 Kluger HM, Tawbi HA, Ascierto ML, *et al*. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. *J Immunother Cancer* 2020;8:e000398.
24 Rizvi N, Ademuyiwa FO, Cao ZA, *et al*. Society for Immunotherapy of Cancer (SITC) consensus definitions for resistance to combinations of immune checkpoint inhibitors with chemotherapy. *J Immunother Cancer* 2023;11:e005920.
25 Ahn M-J, Lisberg A, Paz-Ares L, *et al*. LBA12 Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase III study TROPION-Lung01. *Ann Oncol* 2023;34:S1305–6.
26 Borghaei H, de Marinis F, Dumoulin D, *et al*. SAPPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *Ann Oncol* 2024;35:66–76.
27 Garassino MC, Reznick D, Liu SY, *et al*. EVOKE-01: A phase 3 study of sacituzumab govitecan (SG) versus docetaxel in patients with

non–small cell lung cancer (NSCLC) progressing on or after platinum-based chemotherapy and checkpoint inhibitors. *J Clin Oncol* 2022;40:TPS9149.
28 Neal J, Pavlakis N, Kim S-W, *et al*. CONTACT-01: A randomized phase III trial of atezolizumab + cabozantinib versus docetaxel for metastatic non-small cell lung cancer after a checkpoint inhibitor and chemotherapy. *J Clin Oncol* 2024;42:2393–403.
29 Peled N, Mazieres J, Kowalski DM, *et al*. 121P MK-7684A (vibostolimab [vibo] plus pembrolizumab [pembro] coformulation) with/without docetaxel in metastatic NSCLC after platinum-chemotherapy (chemo) and immunotherapy. *IOTECH* 2023;20:100593.
30 Reckamp KL, Redman MW, Dragnev KH, *et al*. Phase II randomized study of ramucirumab and pembrolizumab versus standard of care in advanced non-small-cell lung cancer previously treated with immunotherapy-lung-MAP S1800A. *J Clin Oncol* 2022;40:2295–306.
31 Atkins MB, Ascierto PA, Feltquate D, *et al*. Society for Immunotherapy of Cancer (SITC) consensus definitions for resistance to combinations of immune checkpoint inhibitors with targeted therapies. *J Immunother Cancer* 2023;11:e005923.
32 Besse B, Pons-Tostivint E, Park K, *et al*. Biomarker-directed targeted therapy plus durvalumab in advanced non-small-cell lung cancer: a phase 2 umbrella trial. *Nat Med* 2024;30:716–29.
33 Peters S, Paz-Ares L, Herbst RS, *et al*. Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects. *J Immunother Cancer* 2022;10:e004863.
34 Zhang Z, Liu X, Chen D, *et al*. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. *Sig Transduct Target Ther* 2022;7:258.
35 Zhou C, Chen J, Wu L, *et al*. PL02.04 Phase 3 study of ivonescimab (AK112) vs. pembrolizumab as first-line treatment for PD-L1-positive advanced NSCLC: Primary analysis of HARMONi-2. *J Thorac Oncol* 2024;19:S1.
36 Theelen WSME, Peulen HMU, Lalezari F, *et al*. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: Results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol* 2019;5:1276–82.
37 Pircher A, Sótér S, Eaton M, *et al*. 117O Stereotactic body radiotherapy (SBRT) with pembrolizumab (pembro) for unresected stage I/II non-small cell lung cancer (NSCLC): The randomized, double-blind, phase III KEYNOTE-867 study. *IOTECH* 2024;24:100746.
38 Antonia SJ, Villegas A, Daniel D, *et al*. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919–29.