SYNOPSIS

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: GSK3359609 **Name of active substance:** GSK3359609 Feladilimab

Study Number: 205801

Title: A Phase II, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants

Investigator(s): Multi-center study

Study Center(s): Forty-four investigative sites in 12 countries

Publication(s): None at the time of this report

Study Period: 24 January 2019 – 23 September 2021

Phase of Development: II

Objectives and Endpoints (Part 1):

Objectives	Endpoints
Primary	
To determine the safety and tolerability of novel regimens	AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
To provide a preliminary evaluation of the efficacy of feladilimab in combination with novel regimens	Objective Response Rate (ORR) Disease Control Rate (DCR)
Characterize the pharmacokinetic properties of feladilimab (ICOS Agonist) or investigational feladilimab combination partners	PK parameters that include C_{max} and C_{min} for feladilimab and in combination (and investigational agent/s included in other arms), as data permit.
Exploratory	
CCI [redacted]	

Objectives and Endpoints (Part 2):

Objectives	Endpoints
Primary	
Determine whether experimental regimens provide evidence for improved survival over SoC therapy	Overall survival as measured by time from randomization to death
Secondary	
Evaluate milestone survival in participants treated with experimental regimens versus SoC therapy for NSCLC	Milestone survival rate at 12 and 18 months
Evaluate other measures of antitumor activity of the experimental regimens compared with SoC therapy for NSCLC (RECIST v1.1 and iRECIST)	CR, PR, SD, PD, PFS, ORR, DoR, DCR iCR, iPR, iUPD, iCPD, iSD iPFS; iORR; iDoR
Evaluate the safety and tolerability of the experimental regimens compared with SoC therapy for NSCLC	Frequency and severity of AEs, AESI; SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and safety assessment parameters, including immunogenicity (ADA)
Characterize the pharmacokinetic properties of feladilimab /SoC, or investigational feladilimab combination partners	PK parameters that may include C_{max} and C_{min} for feladilimab and SoC in combination (and investigational agent/s included in other arms) and for SoC alone, as data permit.
Determine immunogenicity of experimental regimens	ADA incidence for feladilimab and combination partners (where appropriate)
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Note: The prefix "i", used for response related abbreviations in the above table indicates immune responses assigned using iRECIST.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; C_{max} = maximum concentration; C_{min} = minimum concentration; CPD = confirmed progression; CR = complete response; DLT = Dose Limiting Toxicity; DoR = duration of response; CCI [redacted]; ORR = objective response rate; OS = overall survival; CCI [redacted]; PFS = progression-free survival; CCI [redacted] RECIST = Response Evaluation Criteria In Solid Tumors; SAE = serious adverse event; SD = stable disease; SoC = Standard of Care; TMB = Tumor Mutational Burden; UPD = unconfirmed progression.

Methodology:

This was a randomized, Phase 2 open-label platform trial in 2 parts utilizing a Master Protocol designed to investigate the clinical activity of novel experimental regimens compared with current Standard of Care (SoC) regimens in the treatment of patients with relapsed/refractory advanced non-small cell lung cancer (NSCLC) who had failed a prior platinum-containing chemotherapy regimen and an agent targeting programmed cell death protein 1 [PD1] / PD-Ligand 1 [PD-L1] – either in combination or as separate lines. The study evaluated as of the date of this report Part 2 (Arms 1 and 2) and Part 1 (Arm 3), and additional regimens/arms were to be added via protocol amendment(s) (see the Study Design schematic in Figure 1).

The study was structured as a series of substudies that share a common control arm with ongoing updating of the effect size of the control arm through the addition of new participants with each substudy. The study was conducted in 2 parts: Part 1 was an optional, non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. Part 2 was a randomized, Phase 2 study comparing the efficacy and safety of these novel regimens with a SoC arm (referred to as Arm 1 and currently monotherapy docetaxel). Each combination was evaluated in a separate substudy. Each novel combination was first evaluated for safety. This evaluation may have occurred prior to adoption into the Entrée Lung platform study (dose finding in a separate study) or as a distinct substudy within this platform study (Part 1) prior to Part 2. If an experimental regimen met graduation requirements, it advanced to Part 2. As a clarification, the combination was to be tested in a new population to be randomized between the combination and the SoC. The study participants enrolled in Part 1 were not pooled with the study participants in Part 2. The 2 study populations were separate and distinct. Part 1 was open-label single arm, while Part 2 was randomized. Please note that for this Master Protocol, the Parts, the Substudies, and the Arms are all numbered. The Arms are numbered sequentially. Within Part 2, each Substudy is numbered sequentially. Within a Substudy, the Standard of Care Arm is Arm 1 and the combinations are numbered sequentially beginning with Arm 2 in Substudy 1. If a combination enters Part 1 and advances to Part 2, then the Arm number it had in Part 1 will continue to identify that combination in an Arm in a Substudy in Part 2. This schema is summarized in Figure 1.

For the Part 2 randomized survival evaluation, participants were stratified by histology (squamous vs. non-squamous) and line of PD(L)1 therapy (1^{st} vs. 2^{nd} line). Participants with NSCLC with undetermined histology (i.e., NSCLC not otherwise specified) were considered as non-squamous for stratification purposes.

Number of Participants:

As the study used a Master Protocol design, the sample size was not fixed.

A maximum of 15 participants per scheduled regimen were to be enrolled in Part 1; a minimum of 3 participants were to be evaluated for safety before further participants were enrolled.

The initial number of participants for Part 2 in Substudy 1 was estimated to be at least 105 (SoC arm: 35; experimental arm: 70 for Substudy 1). Randomization to SoC/Arm 1 was minimized through an alteration of the randomization ratio once 35 participants were randomized to that arm.

Diagnosis and Main Criteria for Inclusion:

- Histologically or cytologically confirmed diagnosis of NSCLC (squamous or non-squamous) and:
  - Documented disease progression based on radiographic imaging, during or after a maximum of 2 lines of systemic treatment for locally/regionally advanced recurrent, Stage IIIb/Stage IIIc/Stage IV or metastatic disease

    Two components of treatment must have been received in the same line or as separate lines of therapy:

    i. no more than or less than 1 line of platinum-containing chemotherapy regimen, and

    ii. no more than or less than 1 line of PD(L)1 monoclonal antibody (mAb) containing regimen.

Treatment Administration:

The following treatments were to be administered in this study:

- Standard of Care (SoC) or Part 2 Arm 1: Docetaxel 75 mg/m^2 monotherapy intravenous (IV) infusion, once every 3 weeks (Q3W)

- Part 2 Substudy 1, Arm 1 and Arm 2: Docetaxel 75 mg/m^2 monotherapy IV infusion once Q3W compared with feladilimab 80 mg IV infusion once Q3W in combination with docetaxel 75 mg/m^2 IV infusion once Q3W

- Part 1 Arm 3: Feladilimab 24 mg IV once Q3W in combination with ipilimumab 1 mg/kg or 3 mg/kg IV infusion once Q3W

- Part 1 Arm 4: Feladilimab 24 mg IV infusion once Q3W in combination with niraparib 200 mg or 300 mg oral daily

- Part 1 Arm 5: Feladilimab 24 mg IV infusion once Q3W in combination with dostarlimab 500 mg IV infusion and cobolimab 300 mg IV infusion

Proposed Arms 4 and 5 of Part 1 were included in the Protocol but never opened for enrollment.

Statistical Methods:

A maximum of 15 participants per scheduled regimen were to be enrolled in Part 1.

In Part 2 Substudy 1, 70 participants in the experimental arm and a minimum of 35 participants in the SoC arm were to be randomized. Sample size and associated operating characteristics were evaluated via simulation.

The 8-month milestone survival in the SoC arm was estimated to be ~40% in squamous cell lung cancer [Brahmer, 2015], ~60% in non-squamous lung cancer [Borghaei, 2015], and ~50% in PD-L1 positive population [Herbst, 2016]. The participant population in the current study was expected to be a mixed population with both squamous and non-squamous lung cancer participants; therefore, the mean target rate was assumed to be ~50%.

Sample size was chosen by simulating the entire platform in which 4 experimental arms enter the Master Protocol at different points in time. Enrollment of 9 participants per month was assumed. Interim and final analyses were performed based on predetermined decision rules as specified in Section 10.3.3 and Section 10.5.1 of the Protocol, respectively. The planned Phase 3 sample size was 300 (150 participants per arm and a total of 210 events). The future Phase 3 trial using the log-rank (frequentist) test and the decision rule at interim and end of Phase 2 was based on the (Bayesian) predictive probability, given the results in Phase 2 that the future log-rank test in a Phase 3 study will be significant. Therefore, the methodology utilized a mixture of Bayesian and frequentist frameworks. Simulations assessed the Operating Characteristics of the predictive probability decision criteria under the null and alternative hypotheses, as described in Section 10.3.4 of the Protocol. A cutoff of 43% or greater for the predictive probability of success (PoS) of future Phase 3 study, approximately corresponding to an observed hazard ratio (HR) $\leq$0.8 for each substudy, was used as a guide for future development of each experimental arm.

Summary of Results:

Summary of Disposition and Demographics in Part 2 Substudy 1: Docetaxel Monotherapy (SoC) Compared with Feladilimab plus Docetaxel

Overall, 105 participants were included in the Intent-to-Treat (ITT) Population of Part 2 Substudy 1, comparing Arm 1 (SoC docetaxel monotherapy) and Arm 2 (feladilimab plus docetaxel combination therapy). Eighty-seven (83%) participants have died, 11 (10%) participants were in follow-up, and 7 (7%) participants have withdrawn from the study. The primary reason for withdrawal from the study was withdrawal by subject in 5 (5%) participants.

One-hundred four participants received at least 1 dose of study treatment and were included in the Safety Population of Part 2 Substudy 1 (Arm 1 and Arm 2). Seventy participants received treatment with feladilimab in combination with docetaxel, and 34

participants received treatment with docetaxel alone. All 104 participants were discontinued from study treatment. For the participants who received combination therapy of feladilimab plus docetaxel, progressive disease was reported as the primary reason for discontinuation in 49 (70%) participants, followed by adverse events (AEs) in 10 (14%) participants, and physician decision in 6 (9%) participants. For the participants who received docetaxel alone (SoC), 20 (59%) participants were discontinued due to progressive disease, 10 (29%) participants were discontinued due to AEs, and 1 (3%) participant was discontinued due to physician decision.

In Part 2 Substudy 1, the majority of participants were male (76%), white (89%) and not Hispanic (98%). Two (2%) participants were Black or African American. The median age of participants was 64 years (range: 37 to 88 years). Fifty-three (50%) participants were in the age range of 18 to 64 years. Sixty-three percent of participants who received docetaxel alone were in this age group compared to 40% of participants who received feladilimab plus docetaxel in combination. Thirty-five (33%) participants were in the age range of 65 to 74 years. Forty percent of participants who received feladilimab plus docetaxel in combination were in this age group compared with 20% of participants who received docetaxel alone.

In Part 2 Substudy 1, the median time from initial diagnosis to randomization was 18.73 months (range: 3.1 to 118.8 months). Fifty-six (53%) participants had a histology of adenocarcinoma, and 41 (39%) participants had a histology of squamous cell carcinoma. Twenty-nine (28%) participants had a histological grade of poorly differentiated, and 21 (20%) participants had moderately differentiated. Twenty-five (24%) participants had an initial cancer diagnosis of Stage IV, while 18 (17%) participants and 19 (18%) participants had an initial cancer diagnosis of Stage IVa and Stage IVb, respectively.

Summary of Disposition and Demographics in Part 1 Arm 3: Feladilimab and Ipilimumab Combination

Eight participants received at least 1 dose of study treatment and were included in the Safety Population of Part 1 Arm 3 (feladilimab plus ipilimumab combination therapy). As of the completion date (23 September 2021), 4 (50%) participants have died, and 4 (50%) participants were ongoing, of whom 1 (13%) participant was on study treatment and 3 (38%) participants were in follow-up.

Eight participants received at least 1 dose of study treatment in the Safety Population of Part 1 Arm 3. As of the completion date (23 September 2021), 7 (88%) participants were discontinued from study treatment, and 1 (13%) was ongoing. The primary reasons for discontinuation of both study treatments were progressive disease and adverse events in 3 (38%) participants each, and physician decision in 1 (13%) participant.

The majority of participants in Part 1 Arm 3 were male (63%) and white (88%). One (13%) participant was Asian, and 4 (50%) participants were Hispanic or Latino. The median age of participants was 69 years (range: 53 to 80 years). Four (50%) participants were in the age range of 65 to 74 years, and 3 (38%) participants were in the age range of 75 to 84 years.

In Part 1 Arm 3, the median time from initial diagnosis to randomization was 11 months (range: 7.6 to 55.7 months). Five (63%) participants had a histology of adenocarcinoma, and 3 (38%) participants had a histology of squamous cell carcinoma. Two (25%) participants had a histological grade of moderately differentiated, and 1 (13%) participant each had a histological grade of well differentiated and poorly differentiated. There were 4 (50%) participants for whom the histological grade could not be assessed. Three (38%) participants had an initial cancer diagnosis of Stage IV, while 2 (25%) participants each had Stage IVa and Stage IVb, and 1 (13%) participant had Stage IIIa at initial cancer diagnosis.

Summary of Exposure in Part 2 Substudy 1: Docetaxel Monotherapy (SoC) Compared with Feladilimab plus Docetaxel

For the Safety Population in Part 2 Substudy 1, the median number of cycles of feladilimab plus docetaxel combination therapy was 5 cycles (range: 1 to 34 cycles), compared with 4 cycles (range: 1 to 9 cycles) of docetaxel monotherapy. The median relative dose intensity for feladilimab plus docetaxel combination therapy was 83% (range: 33% to 100%), compared with 75.1% (range: 33% to 100%) for docetaxel monotherapy. The median duration of treatment for participants who received feladilimab plus docetaxel combination therapy was 12.4 weeks (range: 0.14 to 104.71 weeks), compared with 9.1 weeks (range: 0.14 to 20.14 weeks) for participants who received docetaxel monotherapy.

Summary of Exposure in Part 1 Arm 3: Feladilimab and Ipilimumab Combination

For the Safety Population in Part 1 Arm 3, the median number of cycles of feladilimab and ipilimumab combination therapy was 2 cycles (range: 1 to 5 cycles). The median relative dose intensity was 100% (range: 50% to 100%). The median duration of treatment was 3.6 weeks (range: 0.14 to 12.4 weeks).

Summary of Efficacy in Part 2 Substudy 1: Docetaxel Monotherapy (SoC) Compared with Feladilimab plus Docetaxel

Overall survival (OS) in the ITT Population of Part 2 Substudy 1 was calculated as the time from randomization to death. For participants who received feladilimab plus docetaxel combination therapy, the median OS was 7.8 months (95% CI: 4.7, 10.8), with 62 (89%) participants who died. For the participants who received docetaxel monotherapy, the median OS was 8.2 months (95% CI: 4.5, 16.1), with 25 (71%) participants who died. The hazard ratio (HR) was 1.5 (95% 92, 2.44). The predictive probability of success of a future Phase 3 study was estimated to be 0.7%.

In Part 2 Substudy 1, the milestone survival rate at 12 months included 28% (95% CI: 18%, 39%) of participants who received feladilimab plus docetaxel combination therapy, compared with 44% (95% CI: 27%, 60%) of participants who received docetaxel monotherapy. The milestone survival rate at 18 months included 18% (95% CI: 10%, 28%) of participants who received feladilimab plus docetaxel combination therapy, compared with 28% (95% CI: 14%, 44%) of participants who received docetaxel monotherapy.

In the ITT Population of Part 2 Substudy 1, the median PFS by RECIST v1.1 for participants who received feladilimab plus docetaxel combination therapy was 3.4 months (95% CI: 2.6, 4.3), compared with 3.3 months (95% CI: 1.6, 4.2) for participants who received docetaxel monotherapy. The HR was 0.84 (95% CI: 0.54, 1.32). Of the participants who received feladilimab plus docetaxel combination therapy, 49 (70%) participants experienced disease progression and 13 (19%) died, compared with 25 (71%) participants who experienced disease progression and 4 (11%) participants who died in the docetaxel monotherapy group.

The disease control rate (CR+PR+SD) in Part 2 Substudy 1 was 50% (95% CI: 37.8%, 62.2%) in participants who received feladilimab plus docetaxel combination therapy, compared with 40% (95% CI: 23.9%, 57.9%) in participants who received docetaxel monotherapy.

In the ITT Population of Part 2 Substudy 1, the confirmed investigator-assessed best response (CR + PR) by RECIST v1.1 was 19% (95% CI: 10.3%, 29.7%) in participants who received feladilimab plus docetaxel combination therapy, compared with 11% (95% CI: 3.2%, 26.7%) in participants who received docetaxel monotherapy. No participants in either treatment group achieved a complete response. Of the participants who received feladilimab plus docetaxel combination therapy, 13 (19%) participants achieved a partial response, 22 (31%) participants achieved stable disease, 23 (33%) participants experienced progressive disease, and 12 (17%) participants were not evaluable. Of the participants who received docetaxel monotherapy, 4 (11%) participants achieved a partial response, 10 (29%) participants achieved stable disease, 14 (40%) participants experienced progressive disease, and 7 (20%) participants were not evaluable.

Summary of Efficacy in Part 1 Arm 3: Feladilimab and Ipilimumab Combination

In the Safety Population of Part 1 Arm 3, no participants who received feladilimab plus ipilimumab achieved a complete response, partial response, or stable disease by RECIST v1.1. Five (63%) participants experienced progressive disease, and 3 (38%) participants were not evaluable.

Summary of Safety in Part 2 Substudy 1: Docetaxel Monotherapy (SoC) Compared with Feladilimab plus Docetaxel

In the Safety Population of Part 2 Substudy 1, all participants experienced at least 1 AE. Overall, 91 (88%) participants experienced AEs considered related to study treatment by the investigator. Twenty-eight (27%) participants experienced AE leading to permanent discontinuation of study treatment. Sixty-nine (66%) participants experienced ≥ Grade 3 AEs. Forty-seven (45%) participants experienced ≥ Grade 3 AEs related to study treatment. Fifty (48%) participants experienced any SAE, and 21 (20%) participants experienced SAEs which were related to study treatment. Ten (10%) participants experienced fatal SAEs, and 3 (3%) participants experienced fatal SAEs which were related to study treatment.

The percentages were comparable between the feladilimab plus docetaxel combination therapy and docetaxel monotherapy with the following exceptions: 12 (35%) participants experienced AEs leading to permanent treatment discontinuation in the docetaxel

monotherapy group, compared with 16 (23%) participants in the feladilimab plus docetaxel combination therapy group; 10 (29%) participants in the docetaxel monotherapy group experienced treatment-related SAEs, compared with 11 (16%) participants in the feladilimab plus docetaxel combination therapy group. Nine (16%) participants in the feladilimab plus docetaxel combination therapy group experienced fatal SAEs, compared with 1 (3%) participant in the docetaxel monotherapy group. All 3 (4%) of treatment-related fatal SAEs occurred in the feladilimab plus docetaxel combination therapy group.

In the Safety Population of Part 2 Substudy 1, 87 (84%) participants overall have died. In the feladilimab plus docetaxel combination treatment group, 62 (89%) participants have died, compared with 25 (74%) participants in the docetaxel monotherapy group. Overall, 74 (71%) participants died due to disease under study. In the feladilimab plus docetaxel combination treatment group, 51 (73%) participants died due to disease under study, compared with 23 (68%) participants in the docetaxel monotherapy group. There were 3 (4%) participants in the feladilimab plus docetaxel combination treatment group who died due to an SAE that was possibly related to study treatment. No participants in the docetaxel monotherapy treatment group experienced a treatment-related SAE resulting in death.

In the Safety Population of Part 2 Substudy 1, 50 (48% of the total exposed population) participants overall experienced at least 1 SAE. In the feladilimab plus docetaxel combination treatment group, 34 (49%) participants experienced an SAE, compared with 16 (47%) participants in the docetaxel monotherapy group. Ten (29%) participants in the docetaxel monotherapy group experienced treatment-related SAEs, compared with 11 (16%) participants in the feladilimab plus docetaxel combination therapy group. Nine (16%) participants in the feladilimab plus docetaxel combination therapy group experienced fatal SAEs, compared with 1 (3%) participant in the docetaxel monotherapy group. All 3 (4%) of treatment-related fatal SAEs occurred in the feladilimab plus docetaxel combination therapy group.

Adverse events of special interest (AESIs) were reported in Part 2 Substudy 1. In the Safety Population of Arm 1 and Arm 2, 5 (5%) participants overall experienced any event of pneumonitis, of which there were 4 participants in the feladilimab plus docetaxel combination therapy group, compared with 1 participant in the docetaxel monotherapy group.

In Arm 2, the feladilimab plus docetaxel combination therapy group, 1 (<1%) participant experienced nephritis (acute kidney injury).

Twelve (12%) participants overall experienced endocrinopathies, including 10 (14%) participants in the feladilimab plus docetaxel combination therapy group (Arm 2), compared with 2 (6%) participants in the docetaxel monotherapy group (Arm 1).

One (<1%) participant in Arm 1, the docetaxel monotherapy group, experienced an infusion-related reaction.

Nine (9%) participants overall experienced an other immune-mediated AE (arthralgia): 6 (9%) participants in Arm 2, the feladilimab plus docetaxel combination therapy group, and 3 (9%) participants in Arm 1, the docetaxel monotherapy group.

Twenty-three (22%) participants overall experienced a skin adverse reaction: 17 (24%) participants in Arm 2, the feladilimab plus docetaxel combination therapy group and 6 (18%) participants in Arm 1, the docetaxel monotherapy group.

No participants experienced an event of colitis, hepatitis, or myocarditis.

Summary of Safety in Part 1 Arm 3: Feladilimab and Ipilimumab Combination

In the Safety Population of Part 1 Arm 3, all participants experienced at least 1 AE. Four (50%) participants each experienced AEs related to study treatment, AEs leading to treatment discontinuation, and AEs ≥ Grade 3. Three (38%) participants experienced at least 1 SAE, and 2 (25%) participants experienced fatal SAEs, neither of which were considered related to study treatment by the investigator. One (13%) participant each experienced a treatment-related SAE and a treatment-related AE ≥ Grade 3.

In the Safety Population of Part 1 Arm 3, 4 (50%) participants died. Two participants died as a result of the disease under study, and 2 participants died as a result of SAEs. One participant experienced a fatal SAE of aspiration pneumonia, and 1 participant experienced a fatal SAE of morphine overdose. Both fatal SAEs were unrelated to study treatment.

Summary of Pharmacokinetics

Feladilimab showed approximately two-fold accumulation in exposure at steady-state consistent with previous Phase I studies. Docetaxel plasma exposure following co-administration with feladilimab was consistent with exposure following monotherapy.

Conclusions:

Part 2 Substudy 1

Primary

- Participants in Arm 2 with NSCLC who received feladilimab plus docetaxel combination therapy did not show an improved overall survival in comparison with participants in Arm 1 who received docetaxel monotherapy (SoC).

Secondary

- Participants in Arm 2 who received feladilimab plus docetaxel combination therapy did not show an improved survival rate at 12 months and 18 months in comparison with participants in Arm 1 who received docetaxel monotherapy (SoC).

- Although no formal statistical test was done, the response rate (CR+PR) in Arm 2 was slightly better than that of Arm 1 in terms of point estimate.

- Although no formal statistical test was done, the disease control rate (CR+PR+SD) in Arm 2 was slightly better than that of Arm 1 in terms of point estimate.

- There were no differences between Arm 1 and Arm 2 for duration of response or progression-free survival.

- Arm 1 and Arm 2 demonstrated an acceptable safety and tolerability profile.

- Feladilimab plasma exposure following co-administration with docetaxel was consistent with exposure after monotherapy from previous studies. Similarly, docetaxel plasma exposure did not change due to co-administration with feladilimab.

Part 1 Arm 3

Primary

- Feladilimab 24 mg plus 1 mg/kg ipilimumab combination therapy demonstrated an acceptable safety and tolerability profile.

Secondary

- No participants who received feladilimab 24 mg plus ipilimumab 1 mg/kg achieved a complete response, partial response, or stable disease.

Effective Date: 16-MAR-2022

SYNOPSIS

Study Title:

A Phase 2, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants.

This clinical study report (CSR) includes the results only from Arm 4 and Arm 5 of Part 1 of the study.

Study Number:

205801

Regulatory Agency Identifier Number(s):

ClinicalTrials.gov:	NCT03739710
EudraCT:	2018-001316-29
IND:	138944

Study Phase:

2

Name of Investigational Intervention:

GSK4428859A

Trade Name:

Belrestotug

Name of Sponsor/Company:

GlaxoSmithKline Research & Development Limited
79 New Oxford Street, London, WC1A 1DG, United Kingdom.

Note that Sponsor address has changed. Prior to the week commencing 16 September 2024 Sponsor address was:

GlaxoSmithKline Research & Development Limited

980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom

Number of Study centers and countries:

This study was conducted at 17 centers in Canada, France, Germany, Italy, Spain, and USA.

Publications (if any):

None at the time of this report.

Study Period:

Study initiation date: 24 January 2019

Study completion date: 02 May 2024

Database lock date: 10 October 2024

Rationale:

While a subset of non-small cell lung cancer (NSCLC) tumors are responsive to immuno-oncology agents, a sizable portion of NSCLC tumors are considered to be intrinsically resistant to said agents, owing in part to its broad immune escape and suppressive features that include low antigenicity, despite having one of the highest frequencies of somatic mutations and a high presence of regulatory T cells (Tregs). However, as shown by the single-agent response rates of anti-programmed cell death protein 1 (PD-1) inhibitors in NSCLC, a subset of tumors is susceptible to T cell-mediated antitumor effects, suggesting those tumors have some degree of prior T-cell immunity. Since effective anti-cancer immune response involves stepwise multistep processes, lung cancers may possess or acquire features that enable them to evade immune surveillance, suppress immune reactivity, proliferate, and survive within an inflammatory microenvironment thereby rendering an immune response ineffectual. Therefore, treatment modalities that incorporate combinations with agents targeting different processes within the immune cascade have the potential to reinstate immunosurveillance; these may include regimens containing chemotherapy that possess advantageous immunological effects to improve clinical efficacy. Patients with NSCLC who have failed both a platinum-containing chemotherapy regimen and an anti-programmed cell death ligand 1 (PD-L1) inhibitor (used either in combination or as separate lines of therapy) have a high unmet medical need for treatment advances with the potential to improve progression-free survival (PFS) and overall survival (OS) forming the basis for evaluation of immuno-oncology combinations in this setting.

Objectives, Endpoints, and Statistical Methods

Objectives and Endpoints (Part 1)

Objectives	Endpoints
Primary	
To determine the safety and tolerability of novel regimen(s)	AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary	
To provide a preliminary evaluation of the efficacy of experimental regimen(s)	Objective Response Rate (ORR) Disease Control Rate (DCR)

Objectives	Endpoints
Characterize the pharmacokinetic properties of experimental regimen(s)	PK parameters that include Cmax and Cmin for experimental regimen(s) (and investigational agent/s included in other arms), as data permit.

AE = adverse event/s; Cmax = maximum observed concentration; Cmin = minimum observed concentration; DLT = Dose Limiting Toxicity' SAE = serious adverse event.

Statistical Methods:

For each experimental regimen, this platform study used a master protocol with distinct arms, and statistical analyses were carried out for each arm independently.

The primary endpoint for Part 1 was the incidence of adverse events (AEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), changes in safety/laboratory assessment parameters, and dose modifications. A key secondary endpoint for Part 1 was ORR using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by investigator assessment.

Methodology:

This was a randomized Phase 2, open-label, platform trial utilizing a master protocol designed to study novel immunotherapy drug combinations compared with the current Standard of Care (SoC), in the treatment of patients with advanced NSCLC who had progressed on prior anti-PD(L)1 and platinum-based combination chemotherapies.

The study was conducted in 2 parts; Part 1 was an open-label, optional, non-randomized part based on safety and pharmacokinetics (PK)/pharmacodynamics evaluation. Part 2 was a randomized, Phase 2, open-label part comparing the efficacy and safety of these novel regimens with SoC.

This CSR includes the results only from Arm 4 and Arm 5 of Part 1 of the study. Combinations evaluated in Arm 4 and Arm 5 were not evaluated in Part 2.

Number of Participants (planned and analyzed):

As the study used a master protocol design, the sample size was not fixed.

In Part 1 Arm 4, a maximum of 24 participants were planned to be enrolled in all dose levels. A minimum of 3 and maximum of 9 participants at each dose level were planned to be evaluated for safety during the 21-day DLT period before enrolling further participants.

CCI [redacted]

A total of 33 participants were screened, of these 6, 9 and 9 participants were enrolled into CCI [redacted] mg, CCI [redacted] mg and CCI [redacted] mg of belrestotug treatment arms respectively with a total of 24 participants enrolled, 19 completed the study and 5 have withdrawn in Part 1 Arm 4.

In Part 1 Arm 5, a minimum of 3 and maximum of 9 participants were planned to be enrolled to DLT (Safety) cohorts for each dose combination. Up to 30 participants were planned to be enrolled across the pharmacokinetics (PK)/pharmacodynamics (Randomized) cohorts within this arm. A maximum sample size of 57 participants were planned to be enrolled in this Arm.

CCI



Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion:

- Histologically or cytologically confirmed diagnosis of NSCLC (squamous or non-squamous) and:
- Documented disease progression based on radiographic imaging, during or after a maximum of 2 lines of systemic treatment for locally/regionally advanced recurrent, Stage IIIb/Stage IIIc/Stage IV or metastatic disease.
- Participants with known BRAF molecular alterations must have had disease progression after receiving the locally available SoC treatment for the molecular alteration.
- Participants who received prior anti-PD(L)1 therapy must had fulfilled the following requirements:
  - Had achieved a complete response (CR), partial response (PR) or stable disease (SD) and subsequently had disease progression (per RECIST 1.1 criteria) either on or after completing PD(L)1 therapy.
  - Had not progressed or recurred within the first 12 weeks of PD(L)1 therapy, either clinically or per RECIST 1.1 criteria.

Exclusion:

- Participants who had received docetaxel at any time.
- Participants who had received >2 prior lines of therapy for NSCLC.

Study Interventions (Arm 4 and Arm 5), Dose, Mode of Administration, and Batch Numbers:

Arm	Treatment
Part 1 Arm 4	Dostarlimab CCI mg CCI in combination with belrestotug CCI mg or CCI mg or CCI mg CCI
Part 1 Arm 5	Dostarlimab CCI mg CCI in combination with belrestotug CCI mg C and GSK6097608 CCI mg or CCI mg or CCI mg CCI

Note: CCI

Batch numbers:

Study intervention	Product Item ID	Product Item Description	Product Lot ID	Product Manufacturing Batch No
Part 1 Arm 4 Note: Investigational product (IP) identified in Arm 4 was also used across Arm 5				
GSK4428859A	CCI	Belrestotug CCI mg/mL / CCI mL vial	CCI	
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		

Study intervention	Product Item ID	Product Item Description	Product Lot ID	Product Manufacturing Batch No
GSK4057190A	CCI	Dostarlimab CCI mg/mL / CCI mL vial	CCI	
GSK4057190A		Dostarlimab CCI mg/mL / CCI mL vial		
Part 1 Arm 5				
GSK6097608B	CCI	Nelistotug CCI mg/mL / CCI mL vial	CCI	
GSK6097608B		Nelistotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4428859A		Belrestotug CCI mg/mL / CCI mL vial		
GSK4057190A		Dostarlimab CCI mg/mL / CCI mL vial		
GSK4057190A		Dostarlimab CCI mg/mL / mL vial		

Duration of Study Intervention:

Combination study treatment was administered at the indicated schedule for a maximum duration of approximately 2 years or up to 35 treatment visits, whichever comes first, or until disease progression as determined by modified RECIST v1.1 for immune-based therapeutics (iRECIST), death, unacceptable toxicity, or other protocol defined criteria were met. After study treatment was permanently discontinued, participants were followed for AEs.

Summary of Results and Conclusions:

Demographic and Other Baseline Characteristics:

In Part 1 Arm 4, the overall median age of the participants was [redacted] years; most participants [redacted]) were <65 years of age. The majority of the participants were male [redacted] participants), White ([redacted] participants) and Not Hispanic or Latino [redacted] participants). The majority of the participants [redacted] participants) had a histology of adenocarcinoma and [redacted]) participants had an initial cancer diagnosis of Stage IVa.

In Part 1 Arm 5 Safety Cohort, the overall median age of the participants was [redacted] years; [redacted]) participants were <65 years of age. The majority of the participants were male [redacted] participants), White [redacted] participants) and Not Hispanic or Latino [redacted] participants). The majority of the participants [redacted] participants) had a histology of adenocarcinoma and [redacted]) participants had an initial cancer diagnosis of Stage IVb.

In Part 1 Arm 5 Randomized Cohort, the overall median age of the participants was [redacted] years; most participants [redacted]) were <65 years of age. The majority of the participants were ma[redacted] participants), White ([redacted] participants) and Not Hispanic or Latino ([redacted] participants). The majority of the participants [redacted] participants) had a histology of adenocarcinoma and [redacted]) participants had an initial cancer diagnosis of Stage IV.

Exposure:

In Part 1 Arm 4, the median number of cycles of belrestotug and dostarlimab for belrestotug plus dostarlimab combination therapy was [redacted] cycles (range: [redacted]). The median relative dose intensity was [redacted]% (range: [redacted] for both belrestotug and dostarlimab. The median actual duration of treatment was [redacted] days (range: [redacted]) for both belrestotug and dostarlimab.

In Part 1 Arm 5 Safety Cohort, the median number of cycles of components for belrestotug plus dostarlimab plus nelistotug combination therapy was [redacted] cycles (range: [redacted]) for both belrestotug and dostarlimab, and [redacted] cycles (range: [redacted] for nelistotug. The median relative dose intensity was [redacted]% (range: [redacted]% (range: [redacted] and [redacted]% (range: [redacted] for belrestotug, nelistotug and dostarlimab, respectively. The median actual duration of treatment was [redacted] days (range: [redacted] for both belrestotug and dostarlimab, [redacted] days (range: [redacted] for nelistotug.

Part 1 Arm 5 Randomized Cohort, the median number of cycles of components, for belrestotug plus dostarlimab plus nelistotug combination therapy was [redacted] cycles (range: [redacted] for all 3 components. The median relative dose intensity was [redacted]% (range: [redacted] for all 3 components. The median actual duration of treatment was [redacted] weeks (range: [redacted]) for all 3 components.

Efficacy Results:

In Part 1 Arm 4, overall, [redacted]%) participants who received belrestotug plus dostarlimab combination therapy reported best response of SD (≥12 weeks) with [redacted]%), [redacted]%) and [redacted]%) participant in each of [redacted] mg, [redacted] mg and [redacted] mg belrestotug treatment arms, respectively. Overall, [redacted]%) participants reported best response of progressive disease (PD) with [redacted]%), [redacted]%) and [redacted]%) participants in [redacted] mg, [redacted] mg and [redacted] mg belrestotug treatment arms respectively. The overall confirmed investigator-assessed ORR by RECIST v1.1 overall, was [redacted]% [redacted]% [redacted]) in participants who received belrestotug plus dostarlimab combination therapy in Part 1 Arm 4. The overall DCR was [redacted]% [redacted] participants [redacted]% CI: [redacted]) in participants who received belrestotug plus dostarlimab combination therapy. [redacted]%), [redacted]%) and [redacted]%) participants had disease control by RECIST v1.1 in the [redacted] mg, [redacted] mg and [redacted] mg belrestotug treatment arms, respectively.

In Part 1 Arm 5 Safety Cohort, overall, [redacted]%) participants who received belrestotug plus dostarlimab plus nelistotug combination therapy reported best response of SD (≥12 weeks) with [redacted]%) and [redacted]%) participants in [redacted] mg and [redacted] mg nelistotug treatment arms, respectively. Overall, [redacted]%) participants reported best response of PD with [redacted]%) participants in the [redacted] mg nelistotug treatment arm and [redacted]%) participants in [redacted] mg nelistotug treatment arm. The confirmed investigator-assessed ORR by RECIST v1.1 overall, was [redacted]% ([redacted]% [redacted] in participants who received belrestotug plus dostarlimab plus nelistotug combination therapy in Part 1 Arm 5 Safety Cohort. The overall DCR was [redacted]% [redacted] participants [redacted]% [redacted]) in participants who received belrestotug plus dostarlimab plus nelistotug combination therapy in Part 1 Arm 5 Safety Cohort. This result was driven by [redacted]%) participants had disease control by RECIST v1.1 in the [redacted] mg nelistotug treatment arm and [redacted]%) participant in the [redacted] mg nelistotug treatment arm.

In Part 1 Arm 5 Randomized Cohort, overall, [redacted]%) participant who received belrestotug plus dostarlimab plus nelistotug combination therapy achieved a PR in [redacted] mg nelistotug treatment arm [redacted]%] participant). Overall, [redacted]%) participants reported best response of SD (≥12 weeks), but this was restricted to the [redacted] mg nelistotug treatment arm [redacted]%] participants). Overall, [redacted]%) participants reported best response of PD with [redacted]%) participants in the [redacted] mg nelistotug treatment arm and [redacted]%) participants in the [redacted] mg nelistotug treatment arm. The confirmed investigator-assessed ORR by RECIST v1.1 overall, was [redacted]% ([redacted] participant [redacted]% [redacted]) in participants who received belrestotug plus dostarlimab plus nelistotug combination therapy in Part 1 Arm 5 Randomized Cohort. This result was driven by [redacted]%) participant in the [redacted] mg nelistotug treatment arm who experienced a confirmed PR. The overall DCR was [redacted]% [redacted] participants [redacted]% [redacted] in participants who received belrestotug plus dostarlimab plus nelistotug combination therapy in Part 1 Arm 5 Randomized Cohort.

This result was driven by CCI %) participants who had disease control by RECIST v1.1 in the CCI mg nelistotug treatment arm and none in the CCI mg nelistotug treatment arm.

Safety Results:

Safety data appeared to be broadly consistent across CCI mg, CCI mg and CCI mg belrestotug treatment arms though participant numbers were small.

Part 1, Arm 4

Overall, CCI %) participants experienced treatment-emergent adverse events (TEAEs), and most of the TEAEs reported were Grade 1 and Grade 2. The most frequently reported TEAEs by system organ class (SOC) were General disorders and administration site conditions (CCI %] participants), Musculoskeletal and connective tissue disorders (CCI %] participants), Skin and subcutaneous tissue disorders (CCI %] participants), and Metabolism and nutrition disorders (CCI %] participants). The most frequently reported TEAEs in Part 1 Arm 4 by preferred term (PT) were decreased appetite CCI %] participants), pruritis CCI %] participants), and infusion-related reaction CCI %] participants).

Overall, CCI %) participants experienced serious TEAEs. In the CCI mg belrestotug treatment arm, one case each of immune-mediated myocarditis, ischemic stroke, pneumonia and sepsis was reported across CCI %) participants. In the CCI mg belrestotug treatment arm, CCI %) participants experienced CCI of nephrolithiasis and pneumonia staphylococcal. CCI serious TEAEs were reported in the CCI mg belrestotug treatment arm.

Overall, CCI %) participant experienced an TEAE of immune-mediated myocarditis that was considered as related to study treatment by the investigator and led to permanent discontinuation of study treatment. CCI %) deaths were reported with primary cause of death as disease under. CCI %) deaths occurred in >30 days after the last dose of study treatment and CCI %) death occurred in ≤30 days. CCI of the deaths were considered by the investigator to be related to the study treatment.

Grade 3-5 drug-related TEAEs were experienced by CCI %) participants. Broadly, these TEAEs were reported to similar frequencies across CCI mg and CCI mg belrestotug treatment arms with no TEAEs reported in the CCI mg belrestotug treatment arm. A drug-related non-fatal serious TEAE was experienced by CCI %) participant of immune-mediated myocarditis CCI mg belrestotug treatment arm). CCI drug-related, non-fatal serious TEAEs were reported in the CCI mg CCI CCI mg belrestotug treatment arms. CCI drug-related fatal serious TEAEs were reported in any of the belrestotug dose levels evaluated.

CCI of the participants experienced hepatobiliary laboratory abnormalities. Overall, CCI %) participants had no change/decreased in protein in urine from baseline.

CCI %) participant had an increase of diastolic blood pressure (DBP) to Grade 3, and [redacted] %) participant had an increase of systolic blood pressure (SBP) to Grade 3 worst case post-baseline (worst case post-baseline includes all scheduled and unscheduled visits post baseline). CCI %) participants had a pulse rate increase to >100 beats per minute worst case post-baseline. CCI %) participants had a temperature increase to ≥38.0ºC worst case post-baseline.

Part 1, Arm 5 Safety Cohort

Overall, CCI %) participants experienced TEAEs, and most of the TEAEs reported were Grade 1 and Grade 2. The most frequently reported TEAEs by SOC were General disorders and administration site conditions CCI %] participants), Musculoskeletal and connective tissue disorder CCI %] participants), Respiratory, thoracic and mediastinal disorders CCI %] participants), Skin and subcutaneous tissue disorders CCI %] participants), Gastrointestinal disorders (CCI %] participants). The most frequently reported TEAEs by PT were rash CCI %] participants), rash pruritic CCI %] participants), anaemia CCI %] participants), constipation CCI %] participants), fatigue CCI %] participants), infusion-related reaction CCI %] participants) and pruritis CCI CCI%] participants).

Overall, CCI %) participants experienced serious TEAEs. In the CCI mg nelistotug treatment arm, CCI %) participants experienced CCI of cancer pain, constipation and respiratory failure. In the CCI mg nelistotug treatment arm, CCI [redacted] of COVID-19 pneumonia, dysphagia, epilepsy, febrile neutropenia and pneumonia were reported across CCI %) participants.

Overall, CCI %) participant experienced an TEAE of respiratory failure, resulting in death, that was considered as not related to study treatment by the investigator and led to permanent discontinuation of study treatment. CCI %) deaths were reported with primary cause of death as disease under study and CCI %) death was reported with primary cause of haemorrhage. CCI %) deaths occurred >30 days after the last dose of study treatment and CCI %) deaths occurred ≤30 days.

Grade 3-5 drug-related TEAEs were experienced by CCI %) participant. CCI of colitis and hypophosphataemia were reported in the CCI mg nelistotug treatment arm, with CCI reported in the CCI mg nelistotug treatment arm. CCI of drug-related, non-fatal, Grade 3 myocarditis was reported as an SAE CCI after receiving their last dose CCI). This was not considered treatment-emergent on account of SAE onset after the protocol define reporting period. CCI drug-related fatal serious TEAEs were reported in both nelistotug dose levels evaluated.

CCI %) participant had alkaline phosphatase (ALP) ≥3x upper limit normal (ULN) in CCI mg nelistotug treatment arm. Overall, CCI %) participants had no change/decreased in protein in urine from baseline.

CCI %) participant had an increase of SBP to Grade 3 worst case post-baseline (worst case post-baseline includes all scheduled and unscheduled visits post baseline). CCI CCI %) participants had a pulse rate increase to >100 beats per minute worst case post-

baseline. [CCI] %) participant had a temperature increase to ≥38.0ºC worst case post-baseline.

[CCI] %) participants had no change or any increase in left ventricular ejection fraction worst case post-baseline in [CCI] mg nelistotug treatment arm.

Part 1, Arm 5 Randomized Cohort

Overall, [CCI] %) participants experienced TEAEs, and most of the TEAEs reported were Grade 1 and Grade 2. The Most frequently reported TEAEs by SOC were of General disorders and administration site conditions ([CCI] %] participants), Injury, poisoning and procedural complications [CCI] %] participants), Respiratory, thoracic and mediastinal disorders ([CCI] %] participants), Gastrointestinal disorders [CCI] %] participants) and Investigations [CCI] %]), Nervous system disorders [CCI] %] participants), and Skin and subcutaneous tissue disorder [CCI] %] participants). The [CCI] reported TEAEs by PT were infusion-related reaction [CCI] %] participants), asthenia [CCI] %] participants), nausea [CCI] %] participants), pruritus ([CCI] %] participants), chest pain [CCI] %] participants) and decreased appetite [CCI] %] participants).

Overall, [CCI] %) participants experienced serious TEAEs. In the [CCI] mg nelistotug treatment arm, [CCI] of hyperglycemia, lung disorder, N-terminal prohormone brain natriuretic peptide increased, pleural effusion and sepsis was reported across [CCI] [CCI] %) participants. In the [CCI] mg nelistotug treatment arm, [CCI] of haemorrhage intracranial, infusion-related reaction, respiratory tract infection and strangulated umbilical hernia was reported across [CCI] %) participants.

Overall, [CCI] %) participants experienced TEAEs of alanine aminotransferase increased, aspartate aminotransferase increased, lung disorder and pruritus and all these were considered as related to study treatment by the investigator and led to permanent discontinuation of study treatment. [CCI] %) deaths were reported with primary cause of death as disease under study. [CCI] %) deaths occurred >30 days after the last dose of study treatment and [CCI] %) death occurred in ≤30 days. [CCI] of the deaths were considered by the investigator to be related to the study treatment.

Grade 3-5 drug-related TEAEs were experienced by [CCI] %) participants. [CCI] of dry skin, lipase increased, pruritis and rash erythematous was reported in the [CCI] mg nelistotug treatment arm and [CCI] of alanine aminotransferase increased in the [CCI] mg nelistotug treatment arm. Drug-related non-fatal serious TEAEs were experienced by [CCI] %) participants. These were lung disorder in the [CCI] mg nelistotug treatment arm and infusion-related reaction in the [CCI] mg nelistotug treatment arm. [CCI] drug-related fatal serious TEAEs were reported in both nelistotug dose levels evaluated.

[CCI] %) participant had alanine aminotransferase (ALT) >8xULN in [CCI] mg nelistotug treatment arm. Overall, [CCI] %) participants had no change/decreased in protein in urine from baseline.

[CCI] %) participants had an increase of SBP to Grade 3 worst case post-baseline (worst case post-baseline includes all scheduled and unscheduled visits post baseline).

CCI %) participants had a pulse rate increase to >100 beats per minute worst case post-baseline.

CCI %) participant had maximum QTc Values increase to Grade 3 in worst case post-baseline in CCI mg nelistotug treatment arm. CCI %) participants had >0 to <10 decrease in left ventricular ejection fraction worst case post baseline across both CCI mg and CCI mg nelistotug treatment arms.

Pharmacokinetic Results:

All CCI participants within the 2 arms had PK evaluated in Arm 4 (N=24), Arm 5 – Safety (N=17), and Arm 5 – Randomized (N=21). Data from CCI out of CCI participants were available for PK analysis.

Part 1, Arm 4

Belrestotug geometric mean half-life (t1/2) after the first dose (Day 1/Week 1) for doses of CCI to CCI mg ranged from CCI hours. The Day 1/Week 1 geometric mean (geometric coefficient of variation [%CVb]) Area under the concentration-time curve over the dosing interval (AUC(0-tau)) and maximum concentration (Cmax) at the CCI mg dose level were CCI %) h*µg/mL and CCI %) µg/mL, respectively and exhibited CCI variability.

Belrestotug appeared to have a CCI increase geometric mean AUC(0-tau) and CCI Cmax across the CCI to CCI mg dose range.

Belrestotug geometric mean accumulation ratio of trough concentration (Cpredose) (for cohorts with n>1) ranged from CCI respectively, across the CCI to CCI mg dose range. CCI trend in accumulation ratio relative to dose was observed. The belrestotug accumulation ratio of concentration at the end of infusion (Ceoi) was CCI in Arm 1 Part 4.

Dostarlimab Day 1/Week 1 mean Ceoi ranged from CCI µg/mL, and the Week 4 mean Cpredose ranged from CCI µg/mL.

Dostarlimab geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) were CCI and ranged from CCI respectively, across treatments. CCI in accumulation ratio relative to treatment was observed.

Part 1, Arm 5

For Arm 5 Safety Cohort, belrestotug geometric mean t1/2 at Day 1/Week 1 ranged from CCI hours. The Day 1/Week 1 geometric mean AUC(0-tau) and Cmax at the CCI mg dose levels ranged from approximately CCI h*µg/mL and CCI µg/mL, respectively and CCI % and CCI %, respectively. For Arm 5 Randomized Cohort, belrestotug geometric mean t1/2 at Day 1/Week 1 ranged from CCI hours. The Day 1/Week 1 geometric mean AUC(0-tau) and Cmax at the CCI mg dose levels ranged from approximately CCI h*µg/mL and CCI µg/mL, respectively and CCI

CCI % and CCI %, respectively. CCI

For belrestotug in Arm 5 Safety Cohort, the geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) was CCI and ranged from CCI, respectively, across treatments. In Arm 5 Randomized Cohort, the geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) ranged from CCI and CCI respectively, across treatments. CCI in accumulation ratio relative to treatment was observed.

For Arm 5 Safety Cohort, dostarlimab Day 1/Week 1 mean Ceoi ranged from CCI µg/mL, and the Week 4 Cpredose ranged from CCI µg/mL. For Arm 5 Randomized Cohort the Day 1/Week 1 mean Ceoi ranged from CCI µg/mL, and the Week 4 Cpredose ranged from CCI µg/mL. CCI

For dostarlimab in Arm 5 Safety Cohort the geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) was CCI and ranged from CCI, respectively, across treatments. For dostarlimab in Arm 5 Randomized Cohort, the geometric mean for accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) ranged from CCI and CCI, respectively, across treatments. CCI in accumulation ratio relative to treatment was observed.

For Arm 5 Safety Cohort, nelistotug geometric mean t1/2 at Day 1/Week 1 for doses of CCI to CCI mg ranged from CCI hours. The Day 1/Week 1 geometric mean AUC(0-tau) and Cmax at the CCI mg dose level was approximately CCI h*µg/mL and CCI µg/mL, respectively, and CCI % and CCI %, respectively. For Arm 5 Randomized Cohort the geometric mean nelistotug t1/2 at Day 1/Week 1 for doses of CCI to CCI mg ranged from CCI hours. The Day 1/Week 1 geometric mean AUC(0-tau) and Cmax at the CCI mg dose level was approximately CCI h*µg/mL and CCI µg/mL, respectively and CCI % and CCI %respectively.

Nelistotug appeared to have a CCI in geometric mean AUC(0-tau) and geometric mean Cmax across the CCI to CCI mg dose range (Arm 5-Safety Cohort) and CCI to CCI mg dose range (Arm 5 Randomized).

The nelistotug geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) in Arm 5 Safety Cohort ranged was CCI and ranged from CCI respectively, across the CCI to CCI mg dose range. A CCI in the geometric mean accumulation ratio was observed across the increasing dose range from CCI to CCI mg. In Arm 5 Randomized, the geometric mean accumulation ratio of Ceoi and Cpredose (for cohorts with n>1) was CCI and ranged from CCI, respectively, across the CCI to CCI mg dose range. A CCI in geometric mean accumulation ratio was observed across the increasing dose range from CCI to CCI mg.

Immunogenicity Results:

Part 1 Arm 4, there were 24 participants enrolled and treated with belrestotug and dostarlimab. Of these, CCI participants had at least one immunogenicity sample result and were included in the analysis. Overall, CCI %) participants had treatment-emergent anti-drug antibody (ADA) with belrestotug.

Part 1 Arm 5 Safety Cohort, there were 17 participants enrolled and treated with belrestotug, dostarlimab and nelistotug. Of these, CCI participants had at least one immunogenicity sample result and were included in the analysis. Overall, CCI %) participant with belrestotug and CCI %) participants with nelistotug had treatment-emergent ADA. CCI of the participants had treatment-emergent ADA with dostarlimab.

Part 1 Arm 5 Randomized Cohort, there were 21 participants enrolled and treated with belrestotug, dostarlimab and nelistotug. Of these, CCI participants had at least one immunogenicity sample result with belrestotug, dostarlimab and nelistotug and were included in the analysis. Overall, CCI %) participants with nelistotug had treatment-emergent ADA. CCI of the participants had treatment-emergent ADA with dostarlimab and belrestotug.

Conclusions:

The demographic characteristics of the study participants were consistent with those anticipated in this population. Overall, 24 (6, 9 and 9 participants in CCI CCI and CCI mg belrestotug treatment arms, respectively), 17 (10 and 7 participants in CCI and CCI mg nelistotug treatment arms, respectively) and 21 (11 and 10 participants in CCI and CCI mg nelistotug treatment arms, respectively) participants were included in Part 1 Arm 4 (belrestotug plus dostarlimab combination therapy), Arm 5 Safety Cohort (belrestotug plus dostarlimab plus nelistotug combination therapy) and Arm 5 Randomized Cohort (belrestotug plus dostarlimab plus nelistotug combination therapy), respectively.

With regards to the primary objective of Part 1 Arm 4 (belrestotug plus dostarlimab) and Arm 5 (belrestotug plus dostarlimab plus nelistotug), these combination therapies demonstrated an acceptable safety and tolerability profile.

With regard to the secondary objective in Part 1 Arm 4 and Arm 5, across Arms 4 and 5, PD comprised a CCI proportion of the overall response ranging from CCI % and represented the CCI in Arm 4 (CCI %] participants) and Arm 5 Randomized Cohort (CCI %] participants). Nonetheless, a CCI of participants also experienced SD CCI %] participants in Arm 4, CCI %] participants in Arm 5 Safety Cohort and CCI %] participants in Arm 5 Randomized Cohort). CCI %) participant experienced a PR in the Arm 5 Randomized Cohort. There were CCI CR. These data, collectively suggest the immunotherapy combinations evaluated have CCI in the setting of NSCLC treated previously with anti-PD(L)-1 and platinum chemotherapy.

Belrestotug, dostarlimab, and nelistotug pharmacokinetics exhibited CCI by combination setting (doublet or triplet). Belrestotug

and nelistotug exposures appeared CCI over the CCI to CCI mg and CCI to CCI mg dose range, respectively (where data were available). CCI in accumulation ratio relative to dose was observed for belrestotug. A CCI in accumulation ratio for nelistotug with increasing dose was observed over the CCI to CCI mg dose range.

In Both Arm 4 & Arm 5, the efficacy and safety results were CCI between participants with treatment-unaffected ADA and participants who tested negative at all time points. Furthermore, at this point in time there is CCI of a clinically meaningful impact of pre-existing ADA on any safety or efficacy measures. In summary, overall, the risk for immunogenicity CCI impact on safety, efficacy and PK.

Date and Version of This Report:

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