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SYNOPSIS

Study Title: A Phase 1b/2, Open-Label, Dose-Finding Study to Evaluate Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination With Either Crizotinib or PF-06463922 in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer

Study Number: B9991005 (Javelin Lung 101)

Regulatory Agency or Public Disclosure Identifier Number:

US IND Number: 126,111

NCT ID: NCT02584634

EudraCT Number: 2015-001879-43

Study Phase: Phase 1b/2

Name of Study Intervention: Avelumab, Crizotinib, Lorlatinib

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: Final CSR (Last Participant Last Visit date) Version 1.0,

15 December 2022

Number of Study Center(s) and Investigator(s):

A total of 43 participants were enrolled at 16 sites in 6 countries (2 of the sites in France did not screen any participants). A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Shaw AT, Lee S-H, Ramalingam SS, et al. Avelumab (anti-PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: Phase 1b results from JAVELIN Lung 101. Journal of Clinical Oncology. 2018;36(15_suppl):9008-08.

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Study Period:

Study Initiation Date (First Participant First Visit): 18 December 2015.

Primary Completion Date: 02 February 2021.

Study Completion Date (Last Participant Last Visit): 13 July 2022.

On 05 June 2018, a Dear Investigator Letter was issued to notify the investigational sites that no new participants could be screened or randomized.

Rationale:

The purpose of the study was to assess efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of avelumab + crizotinib combination and avelumab + lorlatinib combination in cohorts of adult participants with locally advanced or metastatic non-small cell lung cancer (NSCLC).

Enrollment in the study was terminated early based on the changing landscape in treatment options for treatment-naïve Anaplastic Lymphoma Kinase (ALK)-positive NSCLC. This decision was not due to any safety concerns or regulatory interactions. All participants on active treatment at the time of the early enrollment termination could continue treatment and follow-up per the protocol. Participants could opt to be transitioned to the B9991046 continuation study if meeting the eligibility criteria.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are presented in Table S1. Only Dose Level 0 (DL0) was studied in both Group A and Group B, and no other doses were explored. The pre-specified criterion to proceed to Phase 2 was not met for Group A. Given the small number of participants in Group B (N=3) who received study intervention in Phase 2, applicable summaries for Phase 1b and Phase 2 were combined.

Efficacy: The full analysis set was used for all efficacy analyses. Summaries were presented separately for Group A and Group B. Best overall response (BOR) was summarized, and objective response rate (ORR) and disease control rate (DCR) were calculated along with the corresponding exact 2-sided 95% confidence intervals (CIs). Progression-free survival (PFS), overall survival (OS), and duration of response (DR) were analyzed by the Kaplan-Meier method while time to tumor response (TTR) was summarized with descriptive statistics.

Safety: Summaries and analyses of the primary safety endpoint were based on the dose-limiting toxicity (DLT)-evaluable analysis set. All other summaries and analyses of safety parameters were based on the safety analysis set by treatment group. Safety data were summarized using appropriate tabulations and descriptive statistics (pooling together participants treated at the maximum tolerated dose [MTD] from both phases of the study).

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Pharmacokinetic: Standard plasma PK parameters for crizotinib and lorlatinib were estimated using non-compartmental analysis. Dose-normalized parameters were reported as appropriate. Descriptive statistics for the PK parameters for crizotinib and PF-06260182 and lorlatinib were provided by dose, cycle, and day of assessment in tabular form.

Crizotinib, PF-06260182, and lorlatinib plasma concentrations were summarized descriptively (n, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by cycle, day and nominal time. Median profiles of crizotinib, PF-06260182, and lorlatinib concentration-time data were plotted by cycle and day using nominal times.

Trough concentration (C_{trough}) and maximum concentration (C_{max}) for avelumab were summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by cycle and day. The trough concentrations for avelumab were plotted for each dose using a box-whisker plot by cycle and day in order to assess the attainment of steady-state.

Immunogenicity: The analyses of immunogenicity data were based on the immunogenicity analysis set by treatment group. Participants were characterized into different anti-drug antibodies (ADA) categories based on the pre-defined criteria.

Biomarker: The biomarker analyses were based on the relevant biomarker analysis sets by treatment group. For each biomarker or set of biomarkers, participants may be classified as positive, negative, or some other category according to scoring algorithms and cut-offs established from external sources. BOR was summarized for each biomarker category if appropriate. The number of responders (participants with BOR of complete response [CR] or partial response [PR]) was tabulated relative to biomarker classifications using a contingency table and a Fisher's exact test may be performed.

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoints
Primary		
Safety (Phase 1b)	• Group A (ALK-negative): To determine MTD and the RP2D of the combination of avelumab with crizotinib • Group B (ALK-positive): To determine the MTD and the RP2D of the combination of avelumab with lorlatinib	• First 2 cycles DLTs for Group A and Group B
Efficacy (Phase 2)	• Group A: To assess ORR per RECIST v1.1 in previously treated locally advanced or metastatic ALK-negative NSCLC participants treated with the combination of avelumab and crizotinib at the RP2D • Group B: To assess ORR and CR rate per RECIST v1.1 in previously untreated locally advanced or metastatic ALK-positive NSCLC participants treated with the combination of avelumab and lorlatinib at the RP2D	• Confirmed OR per RECIST v.1.1 for Group A • Confirmed OR and CR per RECIST v.1.1 for Group B
Secondary		
Safety (Phases 1b and 2)	• To evaluate the safety and tolerability of avelumab in combination with crizotinib (Group A) or with lorlatinib (Group B)	• AEs and laboratory test abnormalities as graded by NCI CTCAE v4.03; vital signs (blood pressure, pulse rate)
Efficacy (Phases 1b and 2)	• To assess antitumor activity of avelumab in combination with crizotinib (Group A) or with lorlatinib (Group B)	• DC, DR, TTR, PFS per RECIST v1.1, and OS.

PK (Phases 1b and 2)	• To characterize the PK of avelumab in combination with crizotinib (Group A) or with lorlatinib (Group B)	• PK parameters of crizotinib, its metabolite PF-06260182, avelumab and lorlatinib were determined as data permitted:
		  • C_{max}, T_{max}, AUC_{tau}, AUC_{last}, CL/F, V_z/F for crizotinib following multiple dosing in the presence of avelumab
		  • C_{max}, T_{max}, AUC_{tau}, $MRAUC_{tau}$, and MRC_{max} for PF-06260182 following multiple dosing in the presence of avelumab
		  • Single and multiple dose PK (C_{max} and C_{trough}, plasma concentration at the end of dosing interval) of avelumab in the presence of crizotinib and lorlatinib
		  • C_{max}, T_{max}, AUC_{tau}, AUC_{last}, CL/F, and V_z/F for lorlatinib following multiple dosing in the presence of avelumab, if data permitted

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Table S1. Study Objectives and Endpoints

Type	Objective	Endpoints
Immunogenicity (Phases 1b and 2)	• To assess the immunogenicity of avelumab	• Avelumab (ADA; nAb): • ADA/nAb titers for avelumab given in combination with crizotinib or lorlatinib
Biomarker (Phases 1b and 2)	• To evaluate candidate predictive biomarkers of sensitivity or resistance to combination therapy in pretreatment tumor tissue	• Tumor tissue biomarkers, including but not limited to, PD-L1 expression and tumor infiltrating CD8+ T cells by IHC
Exploratory (Not Reported)		
Efficacy	• To explore the antitumor effect of avelumab in combination with crizotinib (Group A) or with lorlatinib (Group B) by irRECIST	• irOR per irRECIST
Biomarker	• To explore the predictive and PD characteristics of peripheral blood and additional tumor tissue biomarkers	• Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, DNA, RNA or proteins that may be related to anti-tumor immune response and/or response to or disease progression on avelumab in combination with either crizotinib or lorlatinib, such as TNF-α, IFNγ and/or tissue FoxP3, PD-1, PD-L2

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ALK = Anaplastic Lymphoma Kinase; AUC_{last} = area under the concentration time curve from time of dosing to the last collection time point; AUC_{tau} = area under the plasma concentration time curve during the dosing interval time (tau); CD8= cluster of differentiation 8; CL/F = apparent plasma clearance; C_{max} = maximum concentration; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; C_{trough} = trough concentration; DC = disease control; DLT = dose-limiting toxicity; DR = duration of response; FoxP3 = forkhead box P3; IFNγ = interferon-gamma; IHC = immunohistochemistry; irOR = immune-related objective response; irRECIST = immune-related RECIST; $MRAUC_{tau}$ = metabolite to parent ratio for AUC_{tau}; MRC_{max} = metabolite to parent ratio for C_{max}; MTD = maximum tolerated dose; nAb = neutralizing antibody; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; OR = objective response; ORR = objective response rate; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand-1; PD-L2 = programmed death ligand-2; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; T_{max} = time for C_{max}; TNF-α = Tumor Necrosis Factor alpha; TTR = time to tumor response; V_z/F = apparent volume of distribution.
Summaries for Phase 2 alone were not performed due to the small number of participants receiving study intervention in Phase 2. Summaries were instead based on Phase 1b and Phase 2 combined, if applicable.
Exploratory endpoint analyses were not conducted for this study as enrollment was terminated.

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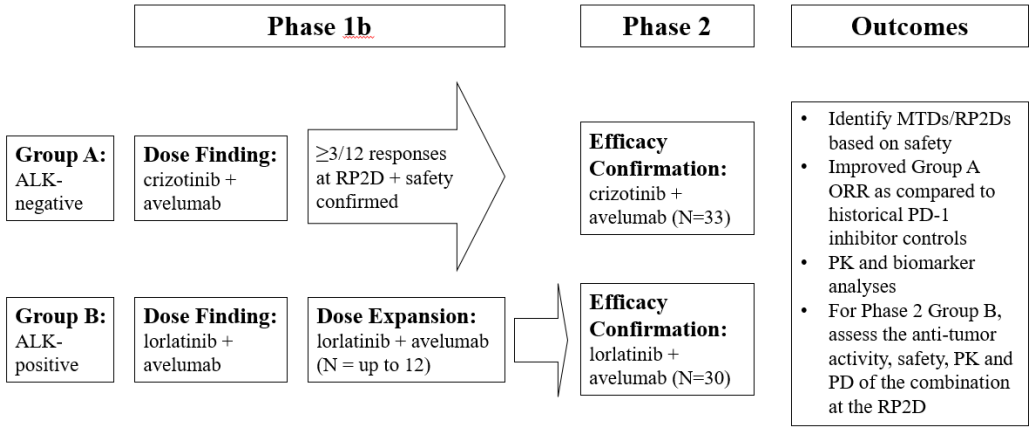
Methodology:

This was a Phase 1b/2, open-label, multi-center, multiple-dose, safety, PK and PD study of Group A (avelumab + crizotinib combination) and Group B (avelumab + lorlatinib combination) in cohorts of adult participants with locally advanced or metastatic NSCLC (Figure S1). The study included Screening, Treatment Period, safety follow-up, and long-term Follow-Up. Safety follow-up period was up to 90 days after the last study treatment. Additional long-term follow-up was collected until death, lost to follow up, study termination by sponsor, or withdrawal by subject.

This is the final clinical study report (CSR) synopsis, reporting data as of last participant last visit (LPLV, ie, 13 July 2022).

Figure S1. Study Schema



Abbreviations: ALK = Anaplastic Lymphoma Kinase; MTD = maximum tolerated dose; ORR = objective response rate; PD = pharmacodynamic(s); PD-1 = programmed death receptor 1; PK = pharmacokinetic(s); RP2D = recommended Phase 2 dose.
Group A (avelumab + crizotinib combination) included the participants with previously treated locally advanced or metastatic ALK-negative NSCLC.
Group B (avelumab + lorlatinib combination) included the participants with locally advanced or metastatic ALK-positive NSCLC. Group B Phase 2 was limited to participants who were treatment-naïve for locally advanced or metastatic disease.

Number of Participants (planned and analyzed):

On 05 June 2018, a Dear Investigator Letter was issued to notify the investigational sites that no new participants could be screened or randomized. Enrollment in the study was terminated early based on the changing landscape in treatment options for treatment-naïve ALK-positive NSCLC. This decision was not due to any safety concerns or regulatory interactions. All participants on active treatment at the time of the early enrollment termination could continue treatment and follow-up per the protocol. A total of 43 participants were enrolled and treated in the study (12 participants in Group A and 31 participants in Group B). The analysis data sets are presented in Table S2.

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Table S2. Analysis Data Sets - All Screened Participants (Protocol B9991005)

	Avelumab 10mg/kg IV Q2W + Crizotinib 250mg PO BID n (%)	Avelumab 10mg/kg IV Q2W + Lorlatinib 100mg PO QD n (%)	Total n (%)
Screened			66
Full analysis set [1]	12	31	43
Safety analysis set [2]	12 (100.0)	31 (100.0)	43 (100.0)
DLT-evaluable analysis set [3]	12 (100.0)	28 (90.3)	40 (93.0)
Avelumab PK concentration analysis set [4]	12 (100.0)	31 (100.0)	43 (100.0)
Crizotinib PK concentration analysis set [4]	12 (100.0)	0	12 (27.9)
Lorlatinib PK concentration analysis set [4]	0	31 (100.0)	31 (72.1)
Crizotinib PK parameter analysis set [5]	10 (83.3)	0	10 (23.3)
Lorlatinib PK parameter analysis set [5]	0	26 (83.9)	26 (60.5)
Immunogenicity analysis set [6]	12 (100.0)	31 (100.0)	43 (100.0)
PD-L1 Biomarker analysis set [7]	9 (75.0)	24 (77.4)	33 (76.7)
CD8 Biomarker analysis set [7]	10 (83.3)	22 (71.0)	32 (74.4)

The denominator to calculate percentages is the number of participants in the full analysis set within each treatment group.
[1] Full analysis set: participants who received at least one dose of study drug.
[2] Safety analysis set: participants who received at least one dose of study drug.
[3] DLT-evaluable analysis set: participants enrolled in phase 1b who are in the safety analysis set, and either experience DLT during the first 2 cycles (28 days), or complete the observation period for the first 2 cycles of treatment.
[4] PK concentration analysis set: participants in the safety analysis set who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab, crizotinib or lorlatinib respectively.
[5] PK parameter analysis set: participants in the safety analysis set who have at least one of the PK parameters of interest for crizotinib or lorlatinib respectively.
[6] Immunogenicity analysis set: participants in the safety analysis set who have at least one ADA/nAb sample result.
[7] Biomarker analysis set: participants in the safety analysis set who have at least one screening biomarker assessment for PD-L1 or CD8 respectively.
PFIZER CONFIDENTIAL SDTM Creation: 10AUG2022 (07:03) Source Data: adsl Table Generation: 02SEP2022 (04:41)
(Cutoff date : 13JUL2022 Snapshot date : 09AUG2022) Output File: ./B9991005/B9991005_CSR/adsl_s002
Table 14.1.1.1 is for Pfizer internal use.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants with locally advanced or metastatic NSCLC; previously treated locally advanced or metastatic ALK-negative-NSCLC for Group A, and locally advanced or metastatic ALK-positive NSCLC for Group B. Group B Phase 2 was limited to participants who were treatment-naïve.

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Study Interventions, Dose, Mode of Administration, and Batch Number(s):

The study interventions used in this study were avelumab, crizotinib and lorlatinib, supplied by Pfizer. The avelumab + crizotinib combination was administered for Group A, and the avelumab + lorlatinib combination for Group B. A cycle was defined as 14 days, regardless of missed doses or dose delays.

- Avelumab was formulated as a 20 mg/mL solution, and intended for intravenous (IV) administration. The starting dose of avelumab was 10 mg/kg IV every 2 weeks (Q2W) for both Group A and Group B.

- Crizotinib was supplied for oral administration as 200 mg or 250 mg capsules. The starting dose of crizotinib in Group A was 250 mg twice daily (BID).

- Lorlatinib was supplied for oral administration as 25 mg tablets. The starting dose of lorlatinib in Group B was 100 mg once daily (QD).

The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S3.

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Table S3. Study Interventions Administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/ Potency	Dosage Form
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	AU018962	18-000772	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1E002	15-002315	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1F004	15-006068	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1F011	16-000913	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1G005	16-004671	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1J001	18-002394	200 mg	Solution
MSB0010718C Solution for Infusion, 20 mg/mL (10 mL/vial)	PD1J008	19-000790	200 mg	Solution
PF-06463922 25 mg Round White Film-Coated Tablet	20-DP-00118	20-000099	25 mg	Tablet
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-002606	25 mg	Tablet
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-004169	25 mg	Tablet
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	15-007544	25 mg	Tablet
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	16-004078	25 mg	Tablet
PF-06463922 25 mg Round White Film-Coated Tablet	N/A	18-002755	25 mg	Tablet

Duration of Study Intervention:

Avelumab, crizotinib and lorlatinib were administered in 14-day cycles. MTD and RP2D were planned to be identified for both Group A and Group B, and a dose expansion was also planned for Group B in Phase 1b. Participants meeting pre-specified criterion were enrolled in Phase 2. Planned duration of study interventions were not defined.

Summary of Results:

Demographic and Other Baseline Characteristics:

The majority of the participants were Asian (58.1% of participants) or White (39.5% of participants). The mean (SD) body weight was 66.3 (17.89) kg. The mean (SD) body mass index (BMI) was 24.2 (5.08) kg/m^2. Most of the histology treated was adenocarcinoma (90.7% of participants). Most participants (40 out of 43) had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

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Exposure:

The median duration of exposure was 15.0 weeks for avelumab and 6.1 weeks for crizotinib in Group A. The median duration of exposure was 42.0 weeks for avelumab and 45.9 weeks for lorlatinib in Group B.

Efficacy Results:

Primary endpoint:

- Of the 12 participants in Group A, no participant had a BOR of confirmed CR and 3 participants had a BOR of confirmed PR. Of the 31 participants in Group B, 1 participant had a BOR of confirmed CR and 15 participants had a BOR of confirmed PR. The confirmed ORR was 25.0% (95% CI: 5.5%, 57.2%) for Group A and 51.6% (95% CI: 33.1%, 69.8%) for Group B.

Secondary endpoints:

- The DCR was 58.3% in Group A, and 71.0% in Group B.

- Of the 12 participants in Group A, 10 (83.3%) participants were reported with a death. The Kaplan-Meier estimate of median OS was 16.4 months (95% CI: 5.4, 27.6). Of the 31 participants in Group B, 15 (48.4%) participants were reported with a death. The Kaplan-Meier estimate of median OS was 32.9 months (95% CI: 10.7, not evaluable [NE]).

- All 12 participants in Group A had a subsequent PFS event (all had progressive disease). The Kaplan-Meier estimate of median PFS was 3.7 months (95% CI: 1.5, 5.5). Of the 31 participants in Group B, 23 (74.2%) had subsequent PFS events (22 had progressive disease and 1 died). The Kaplan-Meier estimate of median PFS was 6.4 months (95% CI: 3.7, 9.2).

- The median TTR was 1.4 months (range: 1.4, 6.9) among 3 responders in Group A and 1.8 months (range: 1.3, 3.7) among 16 responders in Group B.

- All the 3 participants with confirmed CR or PR in Group A had progressive disease. The Kaplan-Meier estimate of median DR was 3.7 months (95% CI: 3.7, 4.6). Of the 16 participants with confirmed CR or PR in Group B, 10 had progressive disease, and none had reported death. The Kaplan-Meier estimate of median DR was 14.7 months (95% CI: 3.7, NE).

Safety Results:

Dose-Limiting Toxicities: Of the 12 DLT-evaluable participants in Group A, 5 (41.7%) participants were reported to have at least 1 DLT. Of the 28 DLT-evaluable participants in Group B, 2 (7.1%) participants were reported to have a DLT. The MTD was exceeded at avelumab 10 mg/kg IV Q2W + crizotinib 250 mg BID orally for Group A, and no dose

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de-escalation was suggested as per the mTPI method. MTD/RP2D was determined as avelumab 10 mg/kg IV Q2W + lorlatinib 100 mg QD orally for Group B. The RP2D was used in Phase 2 for Group B. The pre-specified criterion to proceed to Phase 2 was not met for Group A.

Adverse Events: An overview of the treatment-emergent adverse events (TEAEs) is presented in Table S4.

Table S4. Summary of Adverse Events During the On-Treatment Period - Safety Analysis Set (Protocol B9991005)

Number (%) of Participants	Avelumab 10 mg/kg IV Q2W + Crizotinib 250 mg PO BID (N=12) n (%)	Avelumab 10 mg/kg IV Q2W + Lorlatinib 100 mg PO QD (N=31) n (%)
Participants with TEAEs	12 (100.0)	30 (96.8)
Participants with grade ≥ 3 TEAEs	7 (58.3)	23 (74.2)
Participants with treatment-related TEAEs	12 (100.0)	28 (90.3)
Participants with grade ≥ 3 treatment-related TEAEs	6 (50.0)	16 (51.6)
Participants with serious TEAEs	5 (41.7)	21 (67.7)
Participants with serious treatment-related TEAEs	2 (16.7)	6 (19.4)
Participants with TEAEs leading to discontinuation of avelumab	3 (25.0)	10 (32.3)
Participants with TEAEs leading to discontinuation of crizotinib	6 (50.0)	0
Participants with TEAEs leading to discontinuation of lorlatinib	0	2 (6.5)
Participants with TEAEs leading to discontinuation of any study drug	6 (50.0)	10 (32.3)
Participants with TEAEs leading to discontinuation of all study drugs	3 (25.0)	1 (3.2)
Participants with treatment-related TEAEs leading to discontinuation of avelumab	2 (16.7)	9 (29.0)
Participants with treatment-related TEAEs leading to discontinuation of crizotinib	5 (41.7)	0
Participants with treatment-related TEAEs leading to discontinuation of lorlatinib	0	2 (6.5)
Participants with TEAEs leading to death	1 (8.3)	4 (12.9)
Participants with treatment-related TEAEs leading to death	0	1 (3.2)
Participants with infusion-related reactions (IRRs)	5 (41.7)	9 (29.0)

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Table S4. Summary of Adverse Events During the On-Treatment Period - Safety Analysis Set (Protocol B9991005)

Number (%) of Participants	Avelumab 10 mg/kg IV Q2W + Crizotinib 250 mg PO BID (N=12) n (%)	Avelumab 10 mg/kg IV Q2W + Lorlatinib 100 mg PO QD (N=31) n (%)

The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group.
Treatment-related AEs include AEs related to at least one study drug in the combination.
Any study drug = at least one study drug in the combination. All study drugs = all study drugs in the combination.
MedDRA (v25.0) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 10AUG2022 (07:25) Source Data: adae Table Generation: 26SEP2022 (11:48)
(Cutoff date : 13JUL2022 Snapshot date : 09AUG2022) Output File: ./B9991005/B9991005_CSR/adae_s020
Table 14.3.1.2.1 is for Pfizer internal use.

In Group A, the most frequent all-causality TEAE of any grade was Nausea (7 [58.3%] participants), which was considered to be treatment related in all participants. The most frequent all-causality TEAE of Grade ≥3 was Alanine aminotransferase increased (2 [16.7%] participants), which was considered to be treatment related for both participants.

In Group B, the most frequent all-causality TEAE of any grade was Blood cholesterol increased (19 [61.3%] participants), which was considered to be treatment related in all participants. The most frequent all-causality TEAEs of Grade ≥3 were Lipase increased and Hypertriglyceridaemia (4 [12.9%] participants each). The most frequent treatment-related TEAE of Grade ≥3 was Hypertriglyceridaemia (4 [12.9%] participants).

Ten (83.3%) participants in Group A and 15 (48.4%) participants in Group B died. The primary cause of death was disease progression (6 [50.0%] participants in Group A and 13 [41.9%] participants in Group B). Most deaths (9 out of 10 deaths in Group A and 12 out of 15 deaths in Group B) occurred more than 30 days following the last dose of study intervention. During the on-treatment period, 1 (8.3%) participant in Group A had a TEAE leading to death, which was not considered to be treatment related. Four (12.9%) participants in Group B had TEAEs leading to death, with Dyspnoea for 1 participant considered treatment related.

In Group A, 5 (41.7%) participants experienced all-causality serious adverse events (SAEs). Each SAE was reported in 1 (8.3%) participant. Treatment-related SAEs were reported in 2 (16.7%) participants. In Group B, 21 (67.7%) participants experienced all-causality SAEs. Treatment-related SAEs were reported in 6 (19.4%) participants.

A total of 6 (50.0%) participants in Group A and 10 (32.3%) participants in Group B experienced all-causality TEAEs leading to permanent discontinuation of any study drug.

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Infusion-related reaction (IRRs) of any grade were reported in 5 (41.7%) participants in Group A and 9 (29.0%) participants in Group B. No Grade ≥3 IRRs were reported in Group A, and 1 (3.2%) participant in Group B had Grade ≥3 IRR.

Pharmacokinetic Results:

Avelumab PK: Serum maximum concentrations of avelumab were similar between Cycle 1 Day 1 and Cycle 2 Day 1. Serum trough concentrations of avelumab appeared to reach steady state which were above 10 µg/mL at Cycle 2. The serum concentrations of avelumab tended to be comparable across participants in each treatment group (Group A and Group B).

Crizotinib and Metabolite PF-06260182 PK: Crizotinib and its metabolite PF-06260182 exposures as measured by AUC_{tau} and C_{max} values following co-administration of avelumab were reported. Crizotinib exposure in combination with avelumab was in the range of that following administration of crizotinib alone (historical data). The variability of crizotinib CL/F (based on %CV) was high due to the small sample size.

Lorlatinib PK: Lorlatinib exposures as measured by AUC_{tau}, AUC_{last} and C_{max} values following co-administration of avelumab were reported. Lorlatinib steady-state plasma PK in combination with avelumab was similar to those following administration of lorlatinib alone (historical data).

Other Results:

Biomarker: In Group A, a total of 9 participants were evaluable for programmed death ligand-1 (PD-L1) biomarker analysis; 7 participants were PD-L1 positive and 2 participants were PD-L1 negative. None of the participants evaluable for PD-L1 biomarker analysis in Group A were responders (BOR of CR or PR), regardless of PD-L1 status. The DCR was similar between the PD-L1 positive and negative subgroups (42.9% and 50.0%, respectively).

In Group B, a total of 24 participants were evaluable for PD-L1 biomarker analysis; 20 participants were PD-L1 positive and 4 participants were PD-L1 negative. The ORR was numerically lower in the PD-L1 positive subgroup (50.0%) compared with the PD-L1 negative subgroup (75.0%). The DCR was numerically lower in PD-L1 positive subgroup (65.0%) compared with the PD-L1 negative subgroup (75.0%).

In Group A, a total of 10 participants were evaluable for cluster of differentiation 8 (CD8) biomarker analysis; 6 participants were CD8 positive and 4 participants were CD8 negative. None of the CD8 positive participants evaluable for CD8 biomarker analysis in Group A were responders (BOR of CR or PR). The ORR was 25.0% for the CD8 negative subgroup. The DCR was identical between the CD8 positive and negative subgroups (50.0% for both).

In Group B, a total of 22 participants were evaluable for CD8 biomarker analysis; 4 participants were CD8 positive and 18 participants were CD8 negative. The ORR was higher in the CD8 positive subgroup (50.0%) compared with the CD8 negative subgroup

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(44.4%). The DCR was higher in CD8 positive subgroup (75.0%) compared with the CD8 negative subgroup (61.1%).

Immunogenicity: Among 12 participants with at least one valid post-baseline ADA result and without positive baseline ADA result in Group A, 3 (25.0%) participants developed treatment-induced ADA by avelumab, and of these, 2 participants had persistent ADA response.

Among 30 participants with at least one valid post-baseline ADA result and without positive baseline ADA result in Group B, 6 (20.0%) participants developed treatment-induced ADA by avelumab, and of these, 3 participants had persistent ADA response.

Due to the low observed immunogenicity rate, nAb analysis was not conducted.

Conclusions:

Efficacy

- For Group A (avelumab + crizotinib), minimal anti-tumor activity was observed in participants with locally advanced or metastatic ALK-negative NSCLC.

- For Group B (avelumab + lorlatinib), anti-tumor activity was observed in participants with locally advanced or metastatic ALK-positive NSCLC; however, there were not sufficient data to determine whether this anti-tumor activity was clinically significant when compared to historical lorlatinib monotherapy in participants with treatment-naïve ALK-positive NSCLC.

Safety

- The MTD was exceeded at avelumab 10 mg/kg IV Q2W + crizotinib 250 mg BID orally for Group A, and no dose de-escalation was suggested as per the mTPI method. The MTD/RP2D was determined as avelumab 10 mg/kg IV Q2W + lorlatinib 100 mg QD orally for Group B. The RP2D was used in Phase 2 for Group B. The pre-specified criterion to proceed to Phase 2 was not met for Group A.

- Safety profiles of the combination regimens tested were characterized by manageable toxicities and were generally consistent with the known safety profile of each agent in the combination. No new safety concerns for avelumab, crizotinib or lorlatinib were identified in the treatment combinations on study.

PK

- Co-administration of IV doses of avelumab with multiple oral doses of crizotinib or lorlatinib had no clinically meaningful effect on the exposure of crizotinib or lorlatinib.

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Immunogenicity

- The observed incidence of treatment-induced ADA response to avelumab was 25.0% for avelumab + crizotinib combination and 20.0% for avelumab + lorlatinib combination, which tended to be comparable across other studies.

Biomarker

- There appeared to be no meaningful differences in the proportion of participants in Group A and Group B achieving an objective response whose tumors were PD-L1 positive versus those whose tumors were PD-L1 negative. Similarly, there appeared to be no meaningful differences in the proportion of participants in Group A and Group B with CD8 positive versus CD8 negative cells achieving an objective response. However, due to the small number of participants, a valid conclusion cannot be determined.