Clinical trial results:
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

Summary

EudraCT number	2015-001879-43
Trial protocol	ES
Global end of trial date	13 July 2022

Results information

Result version number	v1 (current)
This version publication date	08 July 2023
First version publication date	08 July 2023

Trial information

Trial identification

Sponsor protocol code	B9991005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02584634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2021
Global end of trial reached?	Yes
Global end of trial date	13 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of avelumab when combined with either crizotinib or lorlatinib (PF-06463922).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	43
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 66 subjects were screened, and 43 subjects were enrolled into the study.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A: Avelumab + Crizotinib

Arm description:

Subjects with locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)-negative non-small cell lung cancer (NSCLC) received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle) and crizotinib 250 mg orally twice a day (BID) on a continuous daily dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The subjects received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle)

Investigational medicinal product name	Crizotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The subjects received crizotinib 250 mg (starting dose) orally twice a day (BID).

Arm title	Group B: Avelumab + Lorlatinib

Arm description:

Subjects with locally advanced or metastatic ALK-positive NSCLC received avelumab 10 mg/kg as a 1-hour IV infusion once every 2 weeks (Day 1 of each cycle) and lorlatinib 100 mg orally once a day (QD) on a continuous daily dosing schedule.

Arm type	Experimental
Investigational medicinal product name	PF-06463922
Investigational medicinal product code	
Other name	Lorlatinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The subjects received PF-06463922 100 mg (starting dose) orally once a day (QD).

Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The subjects received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle)

Number of subjects in period 1	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib
Started	12	31
Completed	0	0
Not completed	12	31
Adverse event, not serious	1	4
Adverse event, serious fatal	-	1
Physician decision	1	2
Consent withdrawn by subject	1	1
Death	-	1
Adverse event, serious non-fatal	2	-
Unspecified	-	6
Progressive disease	7	15
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A: Avelumab + Crizotinib
Reporting group description:	
Subjects with locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)-negative non-small cell lung cancer (NSCLC) received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle) and crizotinib 250 mg orally twice a day (BID) on a continuous daily dosing schedule.	
Reporting group title	Group B: Avelumab + Lorlatinib
Reporting group description:	
Subjects with locally advanced or metastatic ALK-positive NSCLC received avelumab 10 mg/kg as a 1-hour IV infusion once every 2 weeks (Day 1 of each cycle) and lorlatinib 100 mg orally once a day (QD) on a continuous daily dosing schedule.	

Reporting group values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib	Total
Number of subjects	12	31	43
Age Categorical Units: Subjects			
Adults (18-64 years)	9	25	34
Adults (65-84 years)	3	6	9
Adults (85 years and over)	0	0	0
Age Continuous Units: Years			
arithmetic mean	58.67	53.32	
standard deviation	± 10.43	± 11.59	-
Sex: Female, Male Units: Subjects			
Female	6	19	25
Male	6	12	18
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	8	17	25
White	4	13	17
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Unknown	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	11	30	41
Not Reported	1	0	1
Unknown	0	0	0
Age Range Units: Years			
median	59.5	54	
full range (min-max)	43 to 76	30 to 77	-

End points

End points reporting groups

Reporting group title	Group A: Avelumab + Crizotinib

Reporting group description:

Subjects with locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)-negative non-small cell lung cancer (NSCLC) received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle) and crizotinib 250 mg orally twice a day (BID) on a continuous daily dosing schedule.

Reporting group title	Group B: Avelumab + Lorlatinib

Reporting group description:

Subjects with locally advanced or metastatic ALK-positive NSCLC received avelumab 10 mg/kg as a 1-hour IV infusion once every 2 weeks (Day 1 of each cycle) and lorlatinib 100 mg orally once a day (QD) on a continuous daily dosing schedule.

Primary: Number of Subjects With Dose-limiting Toxicities (DLTs): Phase 1b

End point title	Number of Subjects With Dose-limiting Toxicities (DLTs): Phase 1b[1]

End point description:

Any of the following adverse events occurring during the primary DLT observation period (the first 28 days [D]) were classified as DLTs: Grade (G) 4 neutropenia if >7 D; febrile neutropenia; G >=3 neutropenic infection; G >=3 thrombocytopenia with bleeding; G4 thrombocytopenia >7 D; G4 anemia; any G >=3 toxicity, except for any of the following: transient (<=6 h) G3 flu like symptoms or fever; transient (<=24 h) G3 fatigue, local reactions, or headache resolved to G <=1; G3 nausea and/or vomiting, diarrhea or skin toxicity resolved to G <=1 within 7 D; any G >=3 amylase or lipase abnormality; tumor flare phenomenon; single laboratory values out of normal range that weren't related to treatment, didn't have any clinical correlate, and resolve to Grade <=1 within 7 D. The analysis population included all subjects enrolled in Phase 1b who received at least 1 dose of study drug, and either experienced DLT during, or completed the observation period.

End point type	Primary

End point timeframe:

First 2 cycles (1 cycle = 14 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	28		
Units: Subjects	5	2		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Objective Response (OR): Phase 2

End point title	Percentage of Subjects With Objective Response (OR): Phase

End point description:

OR is defined as complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 from the start date until disease progression or death. Both CR and PR were confirmed by repeat assessments performed >=4 weeks after the criteria for response are first met. Per RECIST v1.1: CR was defined as the disappearance of all target or non-target lesions; any pathological lymph nodes (whether target or non-target) had reduction in short axis to <10 mm and all lymph nodes were non-pathological in size (<10 mm short axis). PR was defined as a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study treatment received. If a subject received more than 1 treatment, the subject was classified according to the first treatment received.

End point type	Primary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Percentage of subjects				
number (confidence interval 95%)	25.0 (5.5 to 57.2)	51.6 (33.1 to 69.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With CR for Group B: Phase 2

End point title	Percentage of Subjects With CR for Group B: Phase 2[3][4]

End point description:

Per RECIST v1.1: CR was defined as the disappearance of all target or non-target lesions; any pathological lymph nodes (whether target or non-target) had reduction in short axis to <10 mm and all lymph nodes were non-pathological in size (<10 mm short axis). The analysis population included all subjects who received at least one dose of study drug in Group B. Subjects were classified according to the study treatment actually received. If a subject received more than one treatment the subject was classified according to the first treatment received. Results for Group A are not reported for this end point according to the protocol.

End point type	Primary

End point timeframe:

Baseline up to 60 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this endpoint

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of subjects				
number (not applicable)	3.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point description:

TEAEs are those adverse events (AEs) with onset dates during the on-treatment period for the first time or if the worsening of an AE is during the on-treatment period. Treatment-related (TR) AEs was any untoward medical occurrence attributed to study drug in a subject who received study drug. Per NCI CTCAE v4.03: Grade 3 (G3) events=severe AEs; G4 events=life-threatening consequences, urgent intervention indicated; G5 events=death related to an AE. A serious AE (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged in subject hospitalization; life-threatening experience; persistent or significant disability/incapacity; congenital anomaly. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study drug received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose of study treatment or the day before start day of new anti-cancer therapy (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[5]	31[6]		
Units: Subjects				
Subjects with TEAEs (n=12, 31)	12	30		
Subjects with G >=3 TEAEs (n=12, 31)	7	23		
Subjects with TR TEAEs (n=12, 31)	12	28		
Subjects with G >=3 TR TEAEs (n=12, 31)	6	16		
Subjects with SAEs (n=12, 31)	5	21		
Subjects with TR SAEs (n=12, 31)	2	6		
Subjects Discont A due to TEAEs (n=12, 31)	3	10		
Subjects Discont C due to TEAEs (n=12, 0)	6	99999		
Subjects Discont L due to TEAEs (n=0, 31)	99999	2		
Subjects Discont A, C, or L due to TEAE (n=12, 31)	6	10		

Subjects Discont A, C, and L due to TEAE(n=12, 31)	3	1		
Subjects Discont A due to TR TEAE (n=12, 31)	2	9		
Subjects Discont C due to TR TEAE (n=12, 0)	5	99999		
Subjects Discont L due to TR TEAE (n=0, 31)	99999	2		
Subjects with TEAEs leading to death (n=12, 31)	1	4		
Subjects with TR TEAEs leading to death (n=12, 31)	0	1		
Subjects with infusion-related reactions (n=12,31)	5	9		

Notes:

[5] - 99999=not applicable; Discont.=discontinued; A = avelumab; C= crizotinib; L= lorlatinib

[6] - 99999=not applicable; Discont.=discontinued; A = avelumab; C= crizotinib; L= lorlatinib

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Baseline Laboratory Abnormalities Grade <=2 and Post-Baseline Laboratory Abnormalities of Grades 3 or 4 per NCI CTCAE v4.03

End point title	Number of Subjects with Baseline Laboratory Abnormalities Grade <=2 and Post-Baseline Laboratory Abnormalities of Grades 3 or 4 per NCI CTCAE v4.03

End point description:

The laboratory (lab) results were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 severity grade. G1=mild AE. G2=moderate AE. G3=severe AE. G4=life-threatening consequences; urgent intervention indicated. Shift tables were provided to examine the distribution of lab toxicities. The parameters met the criteria of CTCAE grade shift change from G <=2 at baseline to G3 or 4 post baseline were presented. The analysis population included all subjects who received at least one dose of study drug and who could be evaluated for CTCAE criteria for each parameter in each treatment group. Subjects were classified according to the study treatment received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Screening up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Subjects				
Anemia	0	3		
Lymphocyte count decreased	1	2		
Lymphocyte count increased	0	2		
Neutrophil count decreased	1	0		
White blood cell decreased	1	0		
Alanine aminotransferase increased	3	0		
Aspartate aminotransferase increased	2	1		
Blood bilirubin increased	0	1		

Cholesterol high	0	5		
Creatine phosphokinase increased	0	2		
GGT increased	1	5		
Hypercalcemia	0	2		
Hyperglycemia	1	1		
Hypermagnesemia	0	1		
Hypertriglyceridemia	0	7		
Hypoalbuminemia	0	1		
Hyponatremia	1	3		
Lipase increased	1	5		
Serum amylase increased	0	1		
Hemoglobin increased	0	0		
Platelet count decreased	0	0		
Alkaline phosphatase increased	0	0		
Creatinine increased	0	0		
Hyperkalemia	0	0		
Hypernatremia	0	0		
Hypocalcemia	0	0		
Hypoglycemia	0	0		
Hypokalemia	0	0		
Hypomagnesemia	0	0		
Hypophosphatemia	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Vital Signs Meeting Pre-defined Criteria

End point title	Number of Subjects With Vital Signs Meeting Pre-defined Criteria

End point description:

Pre-defined criteria in vital signs: pulse rate <50 beats per minute (bpm), pulse rate >120 bpm, sitting diastolic blood pressure (DBP) increase and decrease in change from baseline of >= 20 millimeter of mercury (mmHg), sitting systolic blood pressure(SBP) < 90 mmHg, increase and decrease in change from baseline of >= 30mmHg. Baseline is defined as the last assessment prior to the date/time of the first dose of study treatment. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study treatment actually received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Screening up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Subjects				
Pulse rate <50 bpm	2	0		
Pulse rate >120 bpm	0	4		
Sitting DBP change >= 20 mmHg increase	2	13		
Sitting DBP change >= 20 mmHg decrease	5	8		
Sitting SBP <90 mmHg	1	4		
Sitting SBP change >= 30 mmHg increase	1	11		
Sitting SBP change >= 30 mmHg decrease	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR)

End point title	Time to Tumor Response (TTR)

End point description:

TTR is defined, for subjects with an objective response (CR or PR), as the time from the start date (the date of first dose of treatment) to the first documentation of objective response (CR or PR) which is subsequently confirmed. Per RECIST v1.1: CR: disappearance of all non-nodal target lesions and of all non-target lesions. In addition, any pathological lymph nodes assigned as target lesions/ non-target lesions must have a reduction in short axis to <10 mm. PR: at least a 30% decrease in sum of diameter of all target lesions, taking as reference baseline sum of diameters. The analysis population included all subjects who received at least one dose of study drug and who had confirmed complete response or partial response. Subjects were classified according to the study treatment actually received. If a subject received more than one treatment the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	16		
Units: Months				
median (full range (min-max))	1.4 (1.4 to 6.9)	1.8 (1.3 to 3.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

DC is defined as OR (CR or PR) or stable disease (SD) per RECIST v.1.1 from the date of first dose of study treatment until disease progression or death due to any cause. The DCR is the proportion of patients with DC. Per RECIST v1.1: SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD). PD is defined as a >=20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study treatment received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Percentage of subjects				
number (confidence interval 95%)	58.3 (27.7 to 84.8)	71.0 (52.0 to 85.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR: time from first documented occurrence of response (PR or CR) until date of first documented PD or death due to underlying cancer. Subjects with no PD and were still alive by 02 Feb 2020, were censored at last adequate tumor assessment. Kaplan-Meier method was used for DR analysis. The analysis population included all subjects who received at least 1 dose of study drug and who had confirmed complete response or partial response. Subjects were classified according to the study treatment received. If a subject received more than one treatment the subject was classified according to the first treatment received. 99999 = not estimable

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	16		
Units: Month				
median (confidence interval 95%)	3.7 (3.7 to 4.6)	14.7 (3.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the time from start date (the date of first dose of treatment) to the date of the first documentation of PD per RECIST v1.1 or death due to any cause, whichever occurs first. Per RECIST v1.1: PD: a >=20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study treatment actually received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Months				
median (confidence interval 95%)	3.7 (1.5 to 5.5)	6.4 (3.7 to 9.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Overall Survival (OS)

End point title	Kaplan-Meier Estimates of Overall Survival (OS)

End point description:

OS is defined as the time from start date (the date of first dose of treatment) to the date of death due to any cause. The analysis population included all subjects who received at least 1 dose of study drug. Subjects were classified according to the study treatment actually received. If a subject received more than 1 study treatment, the subject was classified according to the first treatment received. 99999 =

not estimable

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle starting Cycle 3, up to end of treatment/withdrawal (maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Months				
median (confidence interval 95%)	16.4 (5.4 to 27.6)	32.9 (10.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Crizotinib in The Presence of Avelumab

End point title	Maximum Plasma Concentration (Cmax) of Crizotinib in The Presence of Avelumab[7]

End point description:

Cmax of crizotinib in the presence of avelumab was observed directly from data. The analysis population included subjects who received at least 1 dose of study drug and who had at least 1 of the pharmacokinetic (PK) parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: nanograms per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)	281 (± 74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Plasma Concentrationtime Curve During The Dosing Interval Time Course (AUCtau) of Crizotinib in The Presence of Avelumab

End point title	Area Under The Plasma Concentrationtime Curve During The Dosing Interval Time Course (AUCtau) of Crizotinib in The Presence of Avelumab[8]

End point description:

AUCtau of crizotinib in the presence of avelumab was caculated by Linear/Log trapezoidal method. Dose interval is defined as after single dose from time zero to the next dose (after single dose and at steady state). The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: nanograms*hours per millilitre (ng*h/mL)				
geometric mean (geometric coefficient of variation)	2755 (± 82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Plasma Clearance (CL/F) of Crizotinib in The Presence of Avelumab

End point title	Apparent Plasma Clearance (CL/F) of Crizotinib in The Presence of Avelumab[9]

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Clearance was estimated from population pharmacokinetic (PK) modeling. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Liters per hour (L/h)				
geometric mean (geometric coefficient of variation)	90.76 (± 82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab

End point title	Cmax of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab[10]

End point description:

Cmax of crizotinib metabolite PF-06260182 in the presence of avelumab was observed directly from data. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	84.11 (± 91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) of Crizotinib in The Presence of Avelumab

End point title	Time to Cmax (Tmax) of Crizotinib in The Presence of Avelumab[11]

End point description:

Tmax of crizotinib in the presence of avelumab was observed directly from data as time of first occurrence. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Hours				
median (full range (min-max))	2.03 (0.00 to 8.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite to Parent Ratio for Cmax (MRCmax) of PF-06260182 in The Presence of Avelumab

End point title	Metabolite to Parent Ratio for Cmax (MRCmax) of PF-06260182 in The Presence of Avelumab[12]

End point description:

MRCmax of metabolite PF-06260182 in the presence of avelumab was caculated (MRCmax=Metabolite Cmax/parent Cmax). Parent=crizotinib, metabolite=PF-06260182. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.2902 (± 25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolite to Parent Ratio for AUCtau (MRAUCtau) of PF-06260182 in The Presence of Avelumab

End point title	Metabolite to Parent Ratio for AUCtau (MRAUCtau) of PF-06260182 in The Presence of Avelumab[13]

End point description:

MRAUCtau of metabolite PF-06260182 in the presence of avelumab was caculated (MRAUCtau=Metabolite AUCtau/parent AUCtau). Parent=crizotinib, metabolite=PF-06260182. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Ratio				
geometric mean (geometric coefficient of variation)	0.2779 (± 33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab

End point title	Tmax of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab[14]

End point description:

Tmax of crizotinib metabolite PF-06260182 in the presence of avelumab was observed directly from data as time of first occurrence. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Hours				
median (full range (min-max))	3.02 (0.00 to 8.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab

End point title	AUCtau of Crizotinib Metabolite PF-06260182 in The Presence of Avelumab[15]

End point description:

AUCtau of crizotinib metabolite PF-06260182 in the presence of avelumab was caculated by Linear/Log trapezoidal method. Dose interval: single dose from time zero to the next dose (after single dose and at steady state). The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for crizotinib in Group A. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6 and 8 hours post dose on Day 1 of Cycle 2

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	789.1 (± 116)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Lorlatinib in The Presence of Avelumab

End point title	Cmax of Lorlatinib in The Presence of Avelumab[16]

End point description:

Cmax of lorlatinib in the presence of avelumab was observed directly from data. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for lorlatinib in Group B. Group A is not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 lorlatinib dose) post dose on Day 1 of Cycle 2

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	596.9 (± 33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Lorlatinib in The Presence of Avelumab

End point title	Tmax of Lorlatinib in The Presence of Avelumab[17]

End point description:

Tmax of lorlatinib in the presence of avelumab was observed directly from data. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for lorlatinib in Group B. Group A is not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 lorlatinib dose) post dose on Day 1 of Cycle 2

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Hours				
median (full range (min-max))	1.23 (0.933 to 4.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Plasma Concentration Time Curve From Time of Dosing to The Last Collection Time Point (AUClast) of Lorlatinib in The Presence of Avelumab

End point title	Area Under The Plasma Concentration Time Curve From Time of Dosing to The Last Collection Time Point (AUClast) of Lorlatinib in The Presence of Avelumab[18]

End point description:

AUClast of lorlatinib in the presence of avelumab. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for lorlatinib in Group B. Group A is not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 lorlatinib dose) post dose on Day 1 of Cycle 2

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	4872 (± 52)			

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F of Lorlatinib in The Presence of Avelumab

End point title	CL/F of Lorlatinib in The Presence of Avelumab[19]

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Clearance was estimated from population PK modeling. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for lorlatinib in Group B. Group A is not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 lorlatinib dose) post dose on Day 1 of Cycle 2

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: L/h				
geometric mean (geometric coefficient of variation)	16.97 (± 44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Avelumab in The Presence of Crizotinib (Group A) or Lorlatinib (Group B) After Single Dose of Avelumab

End point title	Cmax of Avelumab in The Presence of Crizotinib (Group A) or Lorlatinib (Group B) After Single Dose of Avelumab

End point description:

Cmax of avelumab in the presence of crizotinib was observed directly from the data in Group A. Cmax of avelumab in the presence of lorlatinib was observed directly from the data in Group B. The analysis population included subjects who received at least one dose of study drug and who had at least one post-dose concentration measurement above the lower limit of quantification for avelumab.

End point type	Secondary

End point timeframe:

Pre-dose, 1, and 168 hours post dose of avelumab on Cycle 1 Day 1.

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	16		
Units: micrograms/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)	193.2 (± 14)	195.7 (± 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of Lorlatinib in The Presence of Avelumab

End point title	AUCtau of Lorlatinib in The Presence of Avelumab[20]

End point description:

AUCtau of lorlatinib in the presence of avelumab was caculated by Linear/Log trapezoidal method. Dose interval: single dose from time zero to the next dose (after single dose and at steady state). The analysis population included subjects who received at least one dose of study drug and who had at least one of the PK parameters of interest for lorlatinib in Group B. Group A is not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 lorlatinib dose) post dose on Day 1 of Cycle 2

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	5807 (± 42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Avelumab in The Presence of Crizotinib (Group A) or Lorlatinib (Group B) After Multiple Doses of Avelumab

End point title	Cmax of Avelumab in The Presence of Crizotinib (Group A) or Lorlatinib (Group B) After Multiple Doses of Avelumab

End point description:

Cmax of avelumab in the presence of crizotinib was observed directly from the data in Group A. Cmax of avelumab in the presence of lorlatinib was observed directly from the data in Group B. The analysis population included subjects who received at least one dose of study drug and who had at least one post-dose concentration measurement above the lower limit of quantification for avelumab.

End point type	Secondary

End point timeframe:

Pre-dose, 1, and 168 hours post dose of avelumab on Cycle 2 Day 1

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	17		
Units: ug/mL				
geometric mean (geometric coefficient of variation)	174.5 (± 35)	169.4 (± 68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Ctrough) of Avelumab in The Presence of

Crizotinib (Group A) Following Multiple Doses of Avelumab

End point title	Trough Serum Concentration (Ctrough) of Avelumab in The Presence of Crizotinib (Group A) Following Multiple Doses of Avelumab[21]

End point description:

Ctrough is defined as predose concentration following multiple doses. Ctrough of avelumab in the presence of crizotinib was observed directly from the data in Group A. The analysis population included subjects who received at least one dose of study drug and who had least one observation. Number of Subjects Analyzed represents the total number of subjects in the analysis population for this end point. "n" represents the number of subjects with concentration measurement above lower limit of quantification at each visit. Group B was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 2-5, 11, 17, 23, 29, 35, and 47.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group A: Avelumab + Crizotinib			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1 (n=7)	11.76 (± 68)			
Cycle 3 Day 1 (n=6)	16.26 (± 53)			
Cycle 4 Day 1 (n=7)	16.71 (± 34)			
Cycle 5 Day 1 (n=5)	14.21 (± 46)			
Cycle 11 Day 1 (n=2)	26.64 (± 4)			
Cycle 17 Day 1 (n=2)	30.59 (± 9)			
Cycle 23 Day 1 (n=2)	30.63 (± 15)			
Cycle 29 Day 1 (n=2)	30.72 (± 55)			
Cycle 35 Day 1 (n=2)	37.31 (± 27)			
Cycle 47 Day 1 (n=2)	40.91 (± 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Ctrough) of Avelumab in The Presence of Lorlatinib (Group B) Following Multiple Doses of Avelumab

End point title	Trough Serum Concentration (Ctrough) of Avelumab in The Presence of Lorlatinib (Group B) Following Multiple Doses of Avelumab[22]

End point description:

Ctrough is defined as predose concentration following multiple doses. Ctrough of avelumab in the presence of lorlatinib was observed directly from the data in Group B. The analysis population included subjects who received at least one dose of study drug and who had least one observation. Number of Subjects Analyzed represents the total number of subjects in the analysis population for this end point. "n" represents the number of subjects with concentration measurement above lower limit of

quantification at each visit. Group A was not evaluable for this end point.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 2-5, 11, 17, 23, 29, 35, 41, and 47.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistics were reported for the arms specified

End point values	Group B: Avelumab + Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1 (n=22)	16.86 (± 88)			
Cycle 3 Day 1 (n=19)	16.99 (± 116)			
Cycle 4 Day 1 (n=21)	23.71 (± 80)			
Cycle 5 Day 1 (n=16)	26.74 (± 68)			
Cycle 11 Day 1 (n=15)	31.31 (± 71)			
Cycle 17 Day 1 (n=13)	32.69 (± 60)			
Cycle 23 Day 1 (n=11)	33.20 (± 56)			
Cycle 29 Day 1 (n=10)	25.77 (± 66)			
Cycle 35 Day 1 (n=10)	31.27 (± 47)			
Cycle 41 Day 1 (n=7)	30.81 (± 59)			
Cycle 47 Day 1 (n=8)	39.63 (± 64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status

End point description:

ADA never-positive was defined as no positive ADA results at any time point. ADA ever-positive was defined as at least one positive ADA result at any time point. Baseline is defined as the last assessment on or prior to the date/time of the first dose of avelumab. The analysis population was a subset of the safety analysis set (all subjects who received at least one dose of study drug) and included subjects who had at least one ADA sample collected for avelumab.

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1-5, then every 12 weeks thereafter, end of treatment/withdrawal, and 30 days after last avelumab dose (up to a maximum of 5 years)

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	31		
Units: Subjects				
ADA never-positive	9	25		
ADA ever-positive	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Programmed Death Ligand-1 (PD-L1) Biomarker Expression

End point title	Number of Subjects With Positive Programmed Death Ligand-1 (PD-L1) Biomarker Expression

End point description:

PD-L1 protein expression is determined by using Combined Positive Score (CPS), which is the percentage of viable tumor and tumor-infiltrated immune cells (restricted to lymphocytes and macrophages) within or directly associated with tumor cell strands showing partial or complete membrane staining using the SP263 antibody. Positive is defined as CPS>=1% and negative is defined as CPS <1%. The analysis population was a subset of the safety analysis set (all subjects who received at least one dose of study drug) and included subjects who had at least one biomarker parameter of PD-L1 from the corresponding assay sample with at least one baseline biomarker measurement.

End point type	Secondary

End point timeframe:

Baseline

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	24		
Units: Subjects				
Positive	7	20		
Negative	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Tumor Infiltrating CD8+ Lymphocytes

End point title	Number of Subjects With Positive Tumor Infiltrating CD8+ Lymphocytes

End point description:

Tumor infiltrating CD8+ lymphocytes is defined as the number of CD8+ cells per unit area and the percent of counted cells. Positive is defined as >=1% and negative is defined as <1%. The analysis

population was a subset of the safety analysis set (all subjects who received at least one dose of study drug) and included subjects who had at least one biomarker parameter of tumor infiltrating CD8+ lymphocytes from the corresponding assay sample with at least one baseline biomarker measurement.

End point type	Secondary

End point timeframe:

Baseline

End point values	Group A: Avelumab + Crizotinib	Group B: Avelumab + Lorlatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	22		
Units: Subjects				
Positive	6	4		
Negative	4	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days post lost dose of study treatment with a maximum of 5 years.

Adverse event reporting additional description:

The same event may appear as both an AE and an SAE. An event may be categorized as serious in 1 subject and as non-serious in another subject, or 1 subject may have experienced both a serious and non-serious event during the study. Total number at risk below refers to the number of subjects evaluable for SAEs or AEs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Group B: Avelumab + Lorlatinib

Reporting group description:

Subjects with locally advanced or metastatic ALK-positive NSCLC received avelumab 10 mg/kg as a 1-hour IV infusion once every 2 weeks (Day 1 of each cycle) and lorlatinib 100 mg orally once a day (QD) on a continuous daily dosing schedule.

Reporting group title	Group A: Avelumab + Crizotinib

Reporting group description:

Subjects with locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)-negative non-small cell lung cancer (NSCLC) received avelumab 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks (Day 1 of each cycle) and crizotinib 250 mg orally twice a day (BID) on a continuous daily dosing schedule.

Serious adverse events	Group B: Avelumab + Lorlatinib	Group A: Avelumab + Crizotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 31 (67.74%)	5 / 12 (41.67%)	
number of deaths (all causes)	15	10	
number of deaths resulting from adverse events	4	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Superior vena cava occlusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system vasculitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group B: Avelumab + Lorlatinib	Group A: Avelumab + Crizotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 31 (93.55%)	12 / 12 (100.00%)	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	12 / 31 (38.71%)	1 / 12 (8.33%)	
occurrences (all)	18	1	
Peripheral swelling			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Pyrexia			
subjects affected / exposed	5 / 31 (16.13%)	3 / 12 (25.00%)	
occurrences (all)	7	5	
Swelling face			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Oedema			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Mucosal inflammation			
subjects affected / exposed	0 / 31 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Localised oedema			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypothermia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	4 / 31 (12.90%)	1 / 12 (8.33%)	
occurrences (all)	4	3	
Chills			
subjects affected / exposed	2 / 31 (6.45%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Chest pain			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Asthenia			
subjects affected / exposed	3 / 31 (9.68%)	2 / 12 (16.67%)	
occurrences (all)	4	4	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 31 (16.13%)	2 / 12 (16.67%)	
occurrences (all)	6	3	
Cough			
subjects affected / exposed	7 / 31 (22.58%)	1 / 12 (8.33%)	
occurrences (all)	15	1	
Dyspnoea exertional			

subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	8	0	
Lung opacity			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Pneumonitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Productive cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 31 (19.35%)	0 / 12 (0.00%)	
occurrences (all)	7	0	
Hallucination, visual			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Hallucination			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Confusional state			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Restlessness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 31 (29.03%)	4 / 12 (33.33%)	
occurrences (all)	27	10	
Amylase increased			
subjects affected / exposed	3 / 31 (9.68%)	1 / 12 (8.33%)	
occurrences (all)	9	2	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 31 (22.58%)	3 / 12 (25.00%)	
occurrences (all)	25	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Blood cholesterol increased			
subjects affected / exposed	19 / 31 (61.29%)	0 / 12 (0.00%)	
occurrences (all)	72	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 31 (12.90%)	1 / 12 (8.33%)	
occurrences (all)	11	2	
Blood creatinine increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 31 (9.68%)	1 / 12 (8.33%)	
occurrences (all)	11	1	
Hypophonesis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Lipase increased			
subjects affected / exposed	5 / 31 (16.13%)	1 / 12 (8.33%)	
occurrences (all)	14	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	8 / 31 (25.81%)	0 / 12 (0.00%)	
occurrences (all)	12	0	
White blood cell count decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Blood triglycerides increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	6 / 31 (19.35%)	2 / 12 (16.67%)	
occurrences (all)	8	2	
Procedural pain			
subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Fall			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	3	
Atrioventricular block first degree			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 31 (12.90%)	1 / 12 (8.33%)	
occurrences (all)	5	2	
Carpal tunnel syndrome			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 31 (16.13%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Paraesthesia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Neuropathy peripheral			
subjects affected / exposed	7 / 31 (22.58%)	0 / 12 (0.00%)	
occurrences (all)	8	0	
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Lethargy			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Hemiparesis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	4 / 31 (12.90%)	1 / 12 (8.33%)	
occurrences (all)	5	2	
Dysgeusia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Hyperaesthesia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	6 / 31 (19.35%)	3 / 12 (25.00%)	
occurrences (all)	8	7	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Eye disorders			
Keratitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Abdominal pain			
subjects affected / exposed	5 / 31 (16.13%)	1 / 12 (8.33%)	
occurrences (all)	5	1	
Constipation			
subjects affected / exposed	7 / 31 (22.58%)	2 / 12 (16.67%)	
occurrences (all)	10	4	
Dry mouth			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	

Nausea			
subjects affected / exposed	5 / 31 (16.13%)	7 / 12 (58.33%)	
occurrences (all)	6	13	
Oesophageal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	3 / 31 (9.68%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	6 / 31 (19.35%)	6 / 12 (50.00%)	
occurrences (all)	8	12	
Diarrhoea			
subjects affected / exposed	7 / 31 (22.58%)	3 / 12 (25.00%)	
occurrences (all)	12	4	
Proctalgia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Skin hypertrophy			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	5 / 31 (16.13%)	4 / 12 (33.33%)	
occurrences (all)	13	5	
Pruritus			

subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Dry skin			
subjects affected / exposed	4 / 31 (12.90%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Nephropathy toxic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	8 / 31 (25.81%)	0 / 12 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Groin pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Joint swelling			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Muscle spasms			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Muscular weakness			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal pain			

subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	6 / 31 (19.35%)	3 / 12 (25.00%)	
occurrences (all)	7	3	
Pain in extremity			
subjects affected / exposed	4 / 31 (12.90%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Arthralgia			
subjects affected / exposed	13 / 31 (41.94%)	0 / 12 (0.00%)	
occurrences (all)	17	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
Cellulitis			
subjects affected / exposed	3 / 31 (9.68%)	1 / 12 (8.33%)	
occurrences (all)	4	1	
Conjunctivitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Cystitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Lower respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	3 / 31 (9.68%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Rhinitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	

Tooth abscess			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 31 (16.13%)	1 / 12 (8.33%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	2 / 31 (6.45%)	5 / 12 (41.67%)	
occurrences (all)	2	6	
Hypokalaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Hypoglycaemia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 12 (8.33%)	
occurrences (all)	3	5	
Hypertriglyceridaemia			
subjects affected / exposed	18 / 31 (58.06%)	0 / 12 (0.00%)	
occurrences (all)	86	0	
Hyperglycaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Hypercholesterolaemia			
subjects affected / exposed	6 / 31 (19.35%)	0 / 12 (0.00%)	
occurrences (all)	27	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2015	Per request from the United States Food and Drug Administration (US FDA), add statement that patients should have their tumors evaluated for epidermal growth factor receptor (EGFR) mutations and have exhausted appropriate therapy, if positive. Corrected typographical errors within the protocol. Corrected an error on the SOA referring to PF 06463922 PK analysis that was added in error. Corrected an error for hematology and blood chemistry collection in the SOA (Both should occur on Cycles 1 and 2 on Days 1 and 8). Clarified efficiency of decision rules based on mTPI design over traditional 3+3 design. Removed non applicable text related to medical device safety reporting from the Serious Adverse Event section.
24 March 2016	Revised Background, PF-06463922 Dose Modification and Electrocardiograms sections, Exclusion Criteria, and added a new Appendix to address any potential cardiac issues related to PF-06463922. Revised exclusion criteria. Clarified in the inclusion criteria and indication section that Group A patients should be previously treated. Modified inclusion criterion #9 to only include patients with estimated creatinine clearance >30 mL/min. Clarified modified Toxicity Probability Interval dose finding rules including Table 3 and removed previous Appendix 2. Removed Exploratory Objective "To explore changes to the tumor tissue and biomarkers". Revised procedure information, visit time window, and timepoints in the Schedule of Activities and Pharmacokinetic Sample Collection Table. Clarified that baseline signs and symptoms should be collected on the Medical History Case Report Form. Clarified requirements for eye exams, urinalysis, Banked Blood Biospecimen for Exploratory Biomarker Assessments, and Pharmacokinetic sampling. Changed teratogenic risk of PF-06463922 from unknown to known in Section 4.3. Consolidated information for required Banked Biospecimens in Schedule of Assessment and Sections 7.4, 7.5, and 7.5.1. Removed requirement for antineutrophil cytoplasmic antibody, antinuclear antibody and rheumatoid factor testing. Added screening HBV and HCV tests to the Schedule of Activities table. Revised frequency of adrenocorticotropic hormone, Free thyroxine, and thyroid stimulating hormone assessments. Removed requirement for 2 blood pressure readings to be taken 1 hour apart. Updated the Recommended Dose Modifications section. Updated the Management of Avelumab + PF-06463922 Treatment-Related Toxicity guidelines. Combined Sections "Other Prohibited Concomitant Medications and Treatments" and "Other Prohibited Concomitant Medications and Therapies". Additional guidance for use of inhibitors, inducers, and substrates of CYP3A enzymes for Group A was provided.

30 June 2017	Schedule of Assessments and Pharmacokinetic Sample Collection Table: Revised to include tumor sample and blood biospecimes for Group B Phase 2 including new footnote; removed Follow-up Day 30 avelumab PK sample; other clarifications included. Objectives, Endpoints, Study Overview, Study Schema, Sample size calculation, and Efficacy Analyses revised for Group B Phase 2. Inclusion Criterion 2 revised to include requirement of no prior treatment for Group B Phase 2. Inclusion Criterion 6 corrected to state "0 to 2" vs "0 or 2". Exclusion Criterion 3 revised to not apply for Group B Phase 2. Exclusion Criterion 16 revised to update restrictions on cardiovascular disease. Exclusion Criterion 19 updated to restrict listed conditions to within the past 1 year. Exclusion Criterion 22 clarified and Exclusion criteria 24 and 25 added due to emerging data on potential drug interactions with PF-06463922. Administration section for PF-06463922 revised due to emerging food effect data on PF-06463922. Updated Tables 6 and 7 for the management of treatment-related toxicities. Added that PF-06463922 treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline. Revised Section 5.7.1.2 and Table 8 to remove maximum infusion time of 120 minutes. Updated guidance for Inhibitors and Inducers of CYP Enzymes for Group B. Clarification added re: steroid use to specify the guidelines only apply if patient is still receiving avelumab. Table 12: Required Laboratory Tests revised to include corrections and remove redundant language. Clarification of ECG assessment and eliminated redundant language. Collection of Avelumab Pharmacokinetic Samples (Both Groups A and B) and Immunogenicity Assessment sections revised to provide better guidance on collection of avelumab PK and ADA samples, as well as proper sample management.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Enrollment in the study was terminated early based on the changing landscape in treatment options. All subjects on active treatment at the time of the termination could continue treatment and follow up per the protocol.

Notes: