



## 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                            |
| <b>Arm title</b>             | 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).

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | 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)

| <b>Number of subjects in period 1</b> | <b>Group A: Avelumab<br/>+ Crizotinib</b> | <b>Group B: Avelumab<br/>+ Lorlatinib</b> |
|---------------------------------------|---|---|
| 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:<br>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:<br>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: Percentage of Subjects With CR for Group B: Phase 2

|   |   |
|---|---|
| End point title   | Percentage of Subjects With CR for Group B: Phase 2 <sup>[1][2]</sup> |
| End point description:<br>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:<br>Baseline up to 60 months  |   |

#### 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

[2] - 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:<br>Avelumab +<br>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

### 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  $\geq 4$  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  $\geq 30\%$  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:**

[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

| End point values                 | Group A:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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: Number of Subjects With Dose-limiting Toxicities (DLTs): Phase 1b**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Dose-limiting Toxicities (DLTs): Phase 1b <sup>[4]</sup> |
|-----------------|--|

**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  $\geq 3$  neutropenic infection; G  $\geq 3$  thrombocytopenia with bleeding; G4 thrombocytopenia  $> 7$  D; G4 anemia; any G  $\geq 3$  toxicity, except for any of the following: transient ( $\leq 6$  h) G3 flu like symptoms or fever; transient ( $\leq 24$  h) G3 fatigue, local reactions, or headache resolved to G  $\leq 1$ ; G3 nausea and/or vomiting, diarrhea or skin toxicity resolved to G  $\leq 1$  within 7 D; any G  $\geq 3$  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  $\leq 1$  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:**

[4] - 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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

## 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>Lorlatinib |  |  |
|--|--------------------------------------|--------------------------------------|--|--|
| Subject group type                                 | Reporting group                      | Reporting group                      |  |  |
| Number of subjects analysed                        | 12 <sup>[5]</sup>                    | 31 <sup>[6]</sup>                    |  |  |
| 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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  $\geq 20$  millimeter of mercury (mmHg), sitting systolic blood pressure (SBP) < 90 mmHg, increase and decrease in change from baseline of  $\geq 30$  mmHg. 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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 $\geq$ 20 mmHg increase | 2 | 13 |  |  |
| Sitting DBP change $\geq$ 20 mmHg decrease | 5 | 8  |  |  |
| Sitting SBP $<$ 90 mmHg                    | 1 | 4  |  |  |
| Sitting SBP change $\geq$ 30 mmHg increase | 1 | 11 |  |  |
| Sitting SBP change $\geq$ 30 mmHg decrease | 3 | 2  |  |  |

## 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 $\geq$ 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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: 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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: 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  $\geq 20\%$  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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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 <sup>[7]</sup> |
|-----------------|--|

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:<br>Avelumab +<br>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: 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 |
|-----------------|--|



## 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:

[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:<br>Avelumab +<br>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 ( $\pm$ 82)                    |  |  |  |

## 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 <sup>[9]</sup> |
|-----------------|--|

## End point description:

AUCtau of crizotinib in the presence of avelumab was calculated 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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>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: 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 <sup>[10]</sup> |
|-----------------|---|

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:

[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

|                               |                                      |  |  |  |
|-------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>       | Group A:<br>Avelumab +<br>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: 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 <sup>[11]</sup> |
|-----------------|---|

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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>Crizotinib |  |  |  |
| Subject group type                                  | Reporting group                      |  |  |  |
| Number of subjects analysed                         | 10                                   |  |  |  |
| Units: ng/mL  |                                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 84.11 ( $\pm$ 91)                    |  |  |  |

## 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 <sup>[12]</sup> |
|-----------------|---|

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:

[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

|                               |                                      |  |  |  |
|-------------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>       | Group A:<br>Avelumab +<br>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 <sup>[13]</sup> |
|-----------------|---|

End point description:

AUCtau of crizotinib metabolite PF-06260182 in the presence of avelumab was calculated 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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>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: 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 <sup>[14]</sup> |
|-----------------|---|

End point description:

MRAUCtau of metabolite PF-06260182 in the presence of avelumab was calculated (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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>Crizotinib |  |  |  |
| Subject group type                                  | Reporting group                      |  |  |  |
| Number of subjects analysed                         | 10                                   |  |  |  |
| Units: Ratio  |                                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.2779 ( $\pm$ 33)                   |  |  |  |

### 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 <sup>[15]</sup> |
|-----------------|---|

End point description:

MRCmax of metabolite PF-06260182 in the presence of avelumab was calculated (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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>Crizotinib |  |  |  |
| Subject group type                                  | Reporting group                      |  |  |  |
| Number of subjects analysed                         | 10                                   |  |  |  |
| Units: Ratio  |                                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 0.2902 ( $\pm$ 25)                   |  |  |  |

### 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 <sup>[16]</sup> |
|-----------------|--|

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:<br>Avelumab +<br>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 <sup>[17]</sup> |
|-----------------|--|

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:<br>Avelumab +<br>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: AUCtau of Lorlatinib in The Presence of Avelumab

|                 |  |
|-----------------|--|
| End point title | AUCtau of Lorlatinib in The Presence of Avelumab <sup>[18]</sup> |
|-----------------|--|

End point description:

AUCtau of lorlatinib in the presence of avelumab was calculated 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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group B:<br>Avelumab +<br>Lorlatinib |  |  |  |
| Subject group type                                  | Reporting group                      |  |  |  |
| Number of subjects analysed                         | 19                                   |  |  |  |
| Units: ng*h/mL                                      |                                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 5807 ( $\pm$ 42)                     |  |  |  |

## 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 <sup>[19]</sup> |
|-----------------|--|

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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group B:<br>Avelumab +<br>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: 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.  |  |

|   |                                      |                                      |  |  |
|---|--------------------------------------|--------------------------------------|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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: CL/F of Lorlatinib in The Presence of Avelumab

|  |  |
|--|--|
| End point title  | CL/F of Lorlatinib in The Presence of Avelumab <sup>[20]</sup> |
| 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:

[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

|   |                                      |  |  |  |
|---|--------------------------------------|--|--|--|
| <b>End point values</b>                             | Group B:<br>Avelumab +<br>Lorlatinib |  |  |  |
| Subject group type                                  | Reporting group                      |  |  |  |
| Number of subjects analysed                         | 19                                   |  |  |  |
| Units: L/h  |                                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 16.97 ( $\pm$ 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 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

|   |                                      |                                      |  |  |
|---|--------------------------------------|--------------------------------------|--|--|
| <b>End point values</b>                             | Group A:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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 ( $\pm$ 35)                    | 169.4 ( $\pm$ 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 <sup>[21]</sup> |
|-----------------|---|

### 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:<br>Avelumab +<br>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 <sup>[22]</sup> |
|-----------------|---|

### 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:<br>Avelumab +<br>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 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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 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:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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 Tumor Infiltrating CD8+ Lymphocytes

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

## 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  $\geq 1\%$  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

| <b>End point values</b>     | Group A:<br>Avelumab +<br>Crizotinib | Group B:<br>Avelumab +<br>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          |  |
| <b>Pneumonia</b>                                |                |                |  |
| 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          |  |
| <b>Clostridium difficile infection</b>          |                |                |  |
| 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          |  |
| <b>Cellulitis</b>                               |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                           | 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%)              |  |
| <b>General disorders and administration site conditions</b> |                                |                                |  |
| <b>Oedema peripheral</b>                                    |                                |                                |  |
| subjects affected / exposed                                 | 12 / 31 (38.71%)               | 1 / 12 (8.33%)                 |  |
| occurrences (all)   | 18                             | 1                              |  |
| <b>Peripheral swelling</b>                                  |                                |                                |  |
| subjects affected / exposed                                 | 2 / 31 (6.45%)                 | 0 / 12 (0.00%)                 |  |
| occurrences (all)   | 5                              | 0                              |  |
| <b>Pyrexia</b>  |                                |                                |  |
| subjects affected / exposed                                 | 5 / 31 (16.13%)                | 3 / 12 (25.00%)                |  |
| occurrences (all)   | 7                              | 5                              |  |
| <b>Swelling face</b>  |                                |                                |  |
| 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<br>subjects affected / exposed<br>occurrences (all)                    | 5 / 31 (16.13%)<br>14 | 1 / 12 (8.33%)<br>1  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 31 (0.00%)<br>0   | 1 / 12 (8.33%)<br>2  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 31 (3.23%)<br>1   | 1 / 12 (8.33%)<br>1  |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 31 (25.81%)<br>12 | 0 / 12 (0.00%)<br>0  |  |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all)    | 0 / 31 (0.00%)<br>0   | 1 / 12 (8.33%)<br>3  |  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)       | 2 / 31 (6.45%)<br>3   | 0 / 12 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications  |                       |                      |  |
| Infusion related reaction<br>subjects affected / exposed<br>occurrences (all)           | 6 / 31 (19.35%)<br>8  | 2 / 12 (16.67%)<br>2 |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 31 (6.45%)<br>2   | 1 / 12 (8.33%)<br>1  |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 31 (6.45%)<br>2   | 0 / 12 (0.00%)<br>0  |  |
| Cardiac disorders   |                       |                      |  |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                | 1 / 31 (3.23%)<br>1   | 1 / 12 (8.33%)<br>3  |  |
| Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 2 / 31 (6.45%)<br>2   | 0 / 12 (0.00%)<br>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<br>subjects affected / exposed<br>occurrences (all)   | 2 / 31 (6.45%)<br>2   | 0 / 12 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders<br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 31 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 6 / 31 (19.35%)<br>8  | 3 / 12 (25.00%)<br>7 |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 31 (3.23%)<br>1   | 1 / 12 (8.33%)<br>1  |  |
| Eye disorders<br>Keratitis<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 31 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1  |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)  | 1 / 31 (3.23%)<br>1   | 1 / 12 (8.33%)<br>1  |  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)       | 2 / 31 (6.45%)<br>2   | 1 / 12 (8.33%)<br>1  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 31 (16.13%)<br>5  | 1 / 12 (8.33%)<br>1  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 7 / 31 (22.58%)<br>10 | 2 / 12 (16.67%)<br>4 |  |
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)  | 0 / 31 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1  |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 31 (6.45%)<br>2   | 0 / 12 (0.00%)<br>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<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 31 (6.45%)<br>2    | 0 / 12 (0.00%)<br>0  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 31 (16.13%)<br>9   | 1 / 12 (8.33%)<br>1  |  |
| Metabolism and nutrition disorders  |                        |                      |  |
| Acidosis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 31 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 2 / 31 (6.45%)<br>2    | 5 / 12 (41.67%)<br>6 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 31 (6.45%)<br>2    | 0 / 12 (0.00%)<br>0  |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 31 (3.23%)<br>1    | 1 / 12 (8.33%)<br>1  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 31 (3.23%)<br>1    | 1 / 12 (8.33%)<br>1  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 31 (6.45%)<br>3    | 1 / 12 (8.33%)<br>5  |  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)             | 18 / 31 (58.06%)<br>86 | 0 / 12 (0.00%)<br>0  |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                    | 2 / 31 (6.45%)<br>4    | 0 / 12 (0.00%)<br>0  |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 6 / 31 (19.35%)<br>27  | 0 / 12 (0.00%)<br>0  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 10 August 2015 | <p>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.</p> <p>Corrected typographical errors within the protocol.</p> <p>Corrected an error on the SOA referring to PF 06463922 PK analysis that was added in error.</p> <p>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).</p> <p>Clarified efficiency of decision rules based on mTPI design over traditional 3+3 design.</p> <p>Removed non applicable text related to medical device safety reporting from the Serious Adverse Event section.</p>   |
| 24 March 2016  | <p>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 &gt;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 adrenocorticotrophic 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.</p> |

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| 30 June 2017 | <p>Schedule of Assessments and Pharmacokinetic Sample Collection Table: Revised to include tumor sample and blood biospecimens 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.</p> |
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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: