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

JAVELIN LUNG 101

STATISTICAL ANALYSIS PLAN – B9991005

Compounds:	MSB0010718C PF-02341066 PF-06463922
Compound Name:	Avelumab Crizotinib PF-06463922
Version:	3.0
Date:	12-Jul-2019

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991005 is based on the Protocol Amendment 03 dated 30-Jun-2017.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
3	12-Jul-2019	Section 3.2.3 "Pharmacokinetic endpoints" – metabolite to parent ratio for CL/F and V_z/F for PF-06260182 following multiple doses are added. Plasma concentration at the end of dosing interval of avelumab is added. Section 3.5.1 "Adverse events" and Section 6.6.1 "Adverse events" – updated the definition of treatment-emergent adverse event to remove the requirements for worsening from baseline or first onset during the on-treatment period. CCI [redacted] Section 5.2 "General Methods" – Table 5 was updated to remove summaries of Group B Phase 2 data alone due to the small number of patients enrolled (N=3). Section 6.2.2.3 "Duration of response" – added details regarding censoring for duration of response since "no adequate baseline assessment" which is used in censoring for PFS analyses is not applicable to analyses of duration of response for patients with objective response. Section 6.2.3 "Pharmacokinetic endpoints" – the box whisker plots of trough concentrations for avelumab, crizotinib and PF-06463922 are removed. Duplication of analysis was removed. Analysis of C_{trough} was added as appropriate. It was added that observed concentration of avelumab, crizotinib and PF-06463922 from this study may be compared with historical observed concentrations when each drug is administered alone. CCI [redacted] Section 6.2.6 "Endpoints for immunogenicity data of avelumab" – detailed analyses of ADA/nAb were added, including patients characterization based on anti-drug antibody results, definition and analysis of time to and duration of ADA response, analysis of patients who are ADA ever positive and patients with treatment-induced ADA, and analyses of PK and safety by immunogenicity status. CCI [redacted] Section 6.5.1.3 "Baseline summaries" – delete detailed analysis pertaining to smoking exposure and years since quitting. Section 6.5.3 "Study treatment compliance and exposure" and Section 6.5.3.1 "Exposure to avelumab" – removed by-cyce summaries for exposure to avelumab. Section 6.5.3.5 "Dose interruptions" – corrected the definition to align with the eCRF data collection. Section 6.5.3.6 "Dose delays" – aligned the intervals to match the protocol-allowed window for dosing. Section 6.6.1 "Adverse events" and Section 6.6.1.3 "Adverse events leading to interruption of study treatment" –added that IRRs will be excluded in the

		analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion. Section 6.6.1.1 "All adverse events" – added summary of TEAE leading to interruption of avelumab, crizotinib and PF-06463922 respectively; removed summary of TEAE excluding SAEs with frequency ≥5% in any treatment group by SOC and PT. Section 6.6.4 "Other significant adverse events" – given the nature of immune-related AEs, summaries of irAE leading to discontinuation of crizotinib, PF-06463922, any study drug and all study drug were removed. Section 6.6.5.1 "Hematology and chemistry parameters" – added summary for patients with newly occurring or worsening laboratory abnormalities; removed lab data summaries by actual values; changed the listing for liver function tests to include only patients with potential Hy's Law. Section 6.6.7 "Electrocardiogram" – removed the summaries based on a population linear regression method. Appendix 1 "Immune-related Adverse Events" – deleted H02C (since ATC code is associated with anti-corticosteroids rather than corticosteroids) and provided additional ATC codes for concomitant medications in Step 4 of the case definition for irAEs. Minor editorial and consistency changes throughout the document.
2	31-Oct-2017	With protocol amendment 03, a Phase 2 portion is included for Group B. Sections 2.1, 2.2, 3.1, 3.2.2, 5.1, 6.1.2, 6.4 have been modified accordingly. In addition, the following updates were made. Section 2 "Introduction" – updated cut-off date for primary analysis. Section 3.4.1 "Study drug, study treatment and baseline definitions" – added definition of end date of study treatment; clarified definition of baseline applies to all analyses; referred to RR instead of heart rate in ECG baseline derivations since the ECG eCRFs collect RR rather than heart rate. Section 3.5.1 "Adverse events" – clarified that the start of anti-cancer drug therapy is used in the definition. Updated that irAE and IRR derivation rules are documented in Appendices. Section 5.1.2 "Decision rules" – clarified that combinations are deemed too toxic as determined by the DLT rate and/or lower than expected doses of the study treatments. Section 5.2 "General Methods" – added a Table 5 "Study Summaries and Tabulations" for overview of the summaries and the tabulations in this study. Section 5.2.8 "Standard derivations and reporting conventions", Section 6.5.1.1 "Demographic characteristics" – removed derivation of BSA since it is not applicable to this study. Section 5.2.5 "Definition of start of new anti-cancer drug therapy", Section 5.2.6 "Definition of start of new anti-cancer therapy", Section 5.2.10 "Adequate baseline tumor assessment", Section 5.2.11 "Adequate post-baseline tumor assessment" were added to provide the details associated with derivations used to define the on-treatment period and censoring in efficacy analyses. Section 5.3.2.4 "Exposure" – deleted the last step in the imputation "The imputed date will be compared with start date of study drug". Section 5.3.3.2 "Death date" – deleted the last step in the imputation "if the day is missing from the date of last contact it will be imputed to 1st day of the month

		and year of last contact only if derived from the 'Survival Follow-up' eCRF page" since not needed. Section 5.3.3.4 "Date of start of new anti-cancer therapy" was added to provide details of imputation rules for incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery). Section 6.1.2 "Objective response as assessed by the Investigator per RECIST v1.1 (Group A and Group B)" – added definition of BOR of non-CR/non-PD for patients without measurable disease at baseline; included additional reasons for NE associated with no baseline assessment and death prior to first post-baseline tumor assessment. Section 6.1.2.1 "Primary analysis", Section 6.2.2 "Efficacy endpoints" –clarified tumor-related endpoints will be analyzed based on investigator assessment. Section 6.1.2.1 "Primary analysis", Section 6.2.2 "Efficacy endpoints", Section 6.2.3 "Pharmacokinetic endpoints", Section 6.2.5 "Biomarker endpoints", Section 6.2.6 "Endpoints for immunogenicity data of avelumab", CCI [redacted] Section 6.5.1 "Baseline summaries" , Section 6.5.2 "Study conduct and patient disposition", Section 6.5.3 "Study treatment compliance and exposure", Section 6.5.4 "Concomitant medications and non-drug treatments", Section 6.5.5 "Subsequent anti-cancer therapies", Section 6.6 "Safety Summaries and Analyses" – clarified summaries and tabulations will be done as described in Table 5. Section 6.2.2.2 "Disease control" – updated definition for disease control to include non-CR/non-PD as per BOR updated definition. Section 6.2.2.5 "Progression-free survival" – updated the allowable time window for tumor assessment to align with protocol amendment 3; provided more details on the analysis of PFS and Time of Follow-Up for PFS; provided more details and hierarchy associated with the derivation of reasons for censoring; also referred consistently to adequate baseline assessments rather than just baseline assessments in censoring rules. Section 6.2.2.6 "Overall Survival" – provided more details on analysis of Time of Follow-Up for OS; provided more details and hierarchy associated with the derivation of reasons for censoring. Section 6.2.5 "Biomarker endpoints" – provided more details on analysis of biomarker endpoints. CCI [redacted] Section 6.4 "Subset Analyses" – clarified ORR and DR (if meaningful) will be summarized by prior anti-cancer therapy (including drug therapy, radiotherapy and surgery). Section 6.5.1.1 "Demographic characteristics" – added Middle East as another possible geographic region and changed the geographic region Australia to Australasia. Section 6.5.1.4 "Prior anti-cancer therapies" – added "not applicable" as a possible outcome category for best response; clarified that prior anti-cancer therapies will be listed together with concomitant and follow-up therapies but with a flag to identify them as prior therapies. Section 6.5.2.1 "Patient disposition" – aligned the wording and summaries to the

		information collected in the disposition pages of the eCRF. Section 6.5.3 "Study treatment compliance and exposure" – provided details regarding cycle derivations and provided formulas for exposure derivations overall and by cycle. Section 6.5.3.4 "Dose reductions" – added dose reduction definition for crizotinib and PF-06463922. Section 6.5.3.5 "Dose interruptions" was added. Section 6.5.3.6 "Dose delays" – added further derivation details; split the summary for no delays from 1-2 days delays. Section 6.5.3.7 "Infusion rate reductions" – added further derivation details. Section 6.5.3.8 "Infusion interruptions" was added. Section 6.5.5 "Subsequent anti-cancer therapies" – updated eCRF pages that will be used for the summary of subsequent anti-cancer therapies. Section 6.6.1 "Adverse events" – added definition of adverse events leading to dose reduction and adverse events leading to interruption of study treatment. Section 6.6.1.1 "All adverse events", Section 6.6.1.4 "Adverse events leading to treatment discontinuation" – added summaries of AEs leading to discontinuation of all study drugs. Section 6.6.1.2 "Adverse events leading to dose reduction" and Section 6.6.1.3 "Adverse events leading to interruption of study treatment" were added. Section 6.6.1.1 "All adverse events", Section 6.6.4 "Other significant adverse events" – removed tabulation for treatment-related irAEs and IRRs; added tabulations for irAEs and IRRs leading to study drug discontinuation. Section 6.6.2 "Deaths" – removed references to primary cause of death since not collected in the eCRF. Section 6.6.5 "Laboratory data" and subsections – changed the formula for corrected calcium to be expressed in SI units; clarified that the denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for the particular summary. Section 6.6.7 "Electrocardiogram" – clarified that the denominator to calculate percentages for each ECG parameter is the number of patients evaluable for the particular summary. Section 6.6.8 "Physical examination" – added details on the summary of physical examination results. Section 8 "References" updated. Section 9 "Appendices" – added appendices with the irAE and IRR derivation rules; deleted data derivation details since included with more details in the exposure section. Minor editorial and consistency changes throughout the document.
1	18-Sep-2015	Not applicable (N/A)

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B9991005. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, pharmacokinetic (PK) data, centrally assessed ALK, ROS1 status, other biomarker data). The primary analysis will include all data up to a cut-off date corresponding to the earliest of 24 months after the last patient receives the first dose of study treatment, death, withdrawal of consent or lost to follow-up. The final analysis of the data will be performed after last patient last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives

Phase 1b Primary Objectives

- Group A (ALK-negative): To determine maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of the combination of avelumab with crizotinib;
- Group B (ALK-positive): To determine the MTD and the RP2D of the combination of avelumab with PF-06463922.

Phase 2 Primary Objectives

- Group A: To assess ORR per RECIST v1.1 in previously treated locally advanced or metastatic ALK-negative non-small cell lung cancer (NSCLC) patients treated with the combination of avelumab and crizotinib at the RP2D;
- Group B: To assess ORR and CR rate per RECIST v1.1 in previously untreated locally advanced or metastatic ALK-positive NSCLC patients treated with the combination of avelumab and PF-06463922 at the RP2D.

Secondary Objectives (both Phase 1b and 2)

- To evaluate the safety and tolerability of avelumab in combination with crizotinib (Group A) or with PF-06463922 (Group B);
- To assess antitumor activity of avelumab in combination with crizotinib (Group A) or with PF-06463922 (Group B);
- To characterize the PK of avelumab in combination with crizotinib (Group A) or with PF-06463922 (Group B);
- To assess the immunogenicity of avelumab;

- To evaluate candidate predictive biomarkers of sensitivity or resistance to combination therapy in pretreatment tumor tissue.

CCI [redacted]

CCI [redacted]

[redacted]

2.2. Study Design

This is a Phase 1b/2, open-label, multi-center, multiple-dose, safety, pharmacokinetic and pharmacodynamic study of Group A and Group B in cohorts of adult patients with locally advanced or metastatic NSCLC (See Figure 1).

Phase 1b:

Both Group A and Group B will be evaluated to identify the MTD and the RP2D. Patients will be treated at dose level 0 (DL0) of the combination. Determination of the MTD will be performed using the modified toxicity probability interval (mTPI) design using dose de-escalation from the approved prescribed dose of crizotinib (250 mg BID), 100 mg QD of PF-06463922, and the RP2D of avelumab (10 mg/kg Q2W). In Group B, a dose expansion will evaluate an additional 12 patients at the MTD/RP2D to further assess the safety, pharmacokinetics, CCI [redacted] antitumor activity of the combination.

Phase 2 Group A:

After the MTD is identified and the RP2D is determined, the 12 patients treated at the RP2D will be considered Stage 1 of Simon's Optimal Two-Stage design.

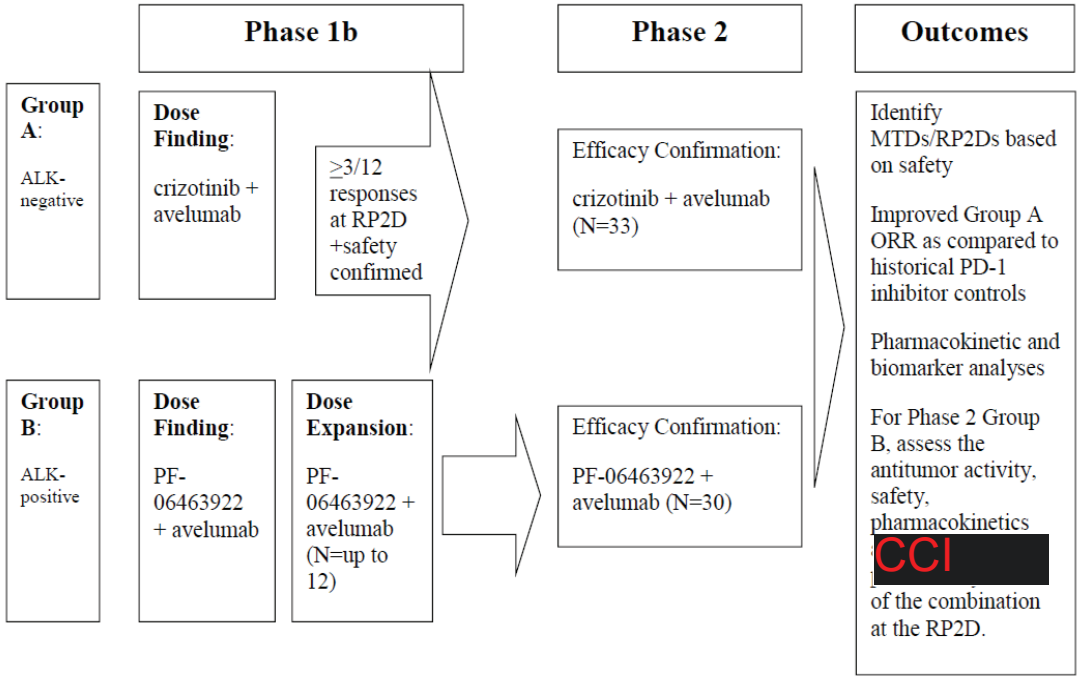
- If ≥3 of the 12 patients in Phase 1b have a confirmed objective response, then an additional 33 patients will be enrolled and treated in Phase 2.
- If ≤2 of the 12 patients in Phase 1b who have a confirmed objective response, then Phase 2 will not be opened for enrollment.

Patients with ALK-negative NSCLC who are enrolled and, subsequently, determined by retrospective central testing to be positive for ALK gene rearrangement, ROS1 gene translocation, c-MET gene amplification, or c-MET exon 14 deletion may be replaced. Patients with NSCLC containing EGFR mutations are permitted onto Group A if they have exhausted appropriate targeted therapy for these mutations.

Phase 2 Group B:

Following the identification of the MTD and determination of the RP2D, approximately 30 additional patients who are treatment-naive will be enrolled in Phase 2, to further assess the antitumor activity, safety, pharmacokinetics CCI [redacted] of the combination at the RP2D.

Figure 1. Study Design Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

Phase 1b:

- First 2 cycles dose-limiting toxicities (DLTs) for Group A and Group B.

  Severity of adverse events (AEs) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For the purpose of dose finding, any of the following AEs occurring during the primary DLT observation period that are attributable to one, the other, or both study drugs will be classified as DLTs:

  Hematologic:

  - Grade 4 neutropenia if >7 days in duration;
  - Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of ≥38.3 degrees C (≥101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour;
  - Grade ≥3 neutropenic infection;
  - Grade ≥3 thrombocytopenia with bleeding;
  - Grade 4 thrombocytopenia >7 days;

- Grade 4 anemia.

Non-Hematologic:

Any Grade ≥3 toxicity, except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management;
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤ 1;
- Grade 3 nausea and/or vomiting that resolves to Grade ≤ 1 within 7 days with appropriate medical management;
- Grade 3 diarrhea or Grade 3 skin toxicity that resolves to Grade ≤ 1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated;
- Any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis;
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor;
- Single laboratory values out of normal range that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management.

Inability to complete at least 75% of crizotinib/PF-06463922 treatment or 2 infusions of avelumab during the DLT observation period due to treatment-related toxicity should be considered a DLT.

While the rules for adjudicating DLTs in the context of dose finding/dose expansion phases are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between Sponsor and Investigator, based on the emerging safety profile.

Phase 2:

- Confirmed Overall Response (OR) per RECIST v1.1 for Group A.
- Confirmed OR and complete response (CR) per RECIST v1.1 for Group B.

  OR is defined as CR or partial response (PR) according to RECIST v1.1 from the date of first dose of study treatment until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- AEs and laboratory abnormalities as graded by NCI CTCAE v4.03; vital signs (blood pressure, pulse rate).

  AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

3.2.2. Efficacy endpoints

- Disease Control (DC), Duration of Response (DR), Time to Tumor Response (TTR), Progression-Free Survival (PFS) per RECIST v1.1, and Overall Survival (OS);

  DC is defined as CR, PR, non-CR/non-PD or SD. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Criteria for SD and non-CR/non-PD must have been met at least 6 weeks after the date of first dose of study treatment.

  DR is defined, for patients with OR, as the time from first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

  TTR is defined, for patients with an OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

  PFS is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

  OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause.

3.2.3. Pharmacokinetic endpoints

- Pharmacokinetic parameters of crizotinib, its metabolite PF-06260182, and avelumab will be determined as data permit:
  - Maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve during the dosing interval time course (AUC_{tau}), area under the plasma concentration-time curve from time of dosing to the last collection time point (AUC_{last}), apparent plasma clearance (CL/F), and apparent volume of distribution (V/F) for crizotinib following multiple dosing in the presence of avelumab;
  - C_{max}, T_{max}, AUC_{tau}, metabolite to parent ratio for AUC_{tau} ($MRAUC_{tau}$), metabolite to parent ratio for C_{max} (MRC_{max}), CL/F, and V_z/F for PF-06260182 following multiple doses in the presence of avelumab;
  - Single and multiple dose pharmacokinetics (C_{max} and C_{trough}, plasma concentration at the end of dosing interval) of avelumab in the presence of crizotinib and PF-06463922.

Table 2. PK Parameters to be Determined for Avelumab, Crizotinib, its metabolite PF-06260182, and PF-06463922

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
$AUC_{sd,\tau}$ $AUC_{ss,\tau}$	Area under the plasma concentration-time profile after single dose from time zero to the time of next dose (after single dose and at steady state)	Linear/Log trapezoidal method
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time to C_{max}	Observed directly from data as time of first occurrence
$t_{½}$ [a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
C_{trough}	Observed plasma concentration at the end of dosing interval	Observed directly from data
CL/F	Apparent clearance	Dose / AUCτ for steady state
V_z/F [a]	Apparent volume of distribution	Dose / (AUCτ ·kel) for steady state
$AUC_{last}(dn)$	Dose normalized AUC_{last}	AUC_{last} / Dose
$AUC_{inf}(dn)$ [a]	Dose normalized AUC_{inf}	AUC_{inf} / Dose
$C_{max}(dn)$	Dose normalized C_{max}	C_{max} / Dose
$MRAUC_{tau}$ [a]	Metabolite to parent ratio for AUC_{tau}	Metabolite $AUC_{tau/parent}$ AUC_{tau}
MRC_{max} [a]	Metabolite to parent ratio for C_{max}	Metabolite $C_{max/parent}$ C_{max}

[a] If data permit

3.2.4. Immunogenicity endpoints

- Avelumab anti-drug antibodies (ADA; neutralizing antibodies).

  ADA / Neutralizing antibodies (nAb) titers for avelumab given in combination with crizotinib or PF-06463922.

3.2.5. Biomarker endpoints

- Tumor tissue biomarkers, including but not limited to, PD-L1 expression and tumor infiltrating CD8+ T cells by immunohistochemistry (IHC).

Table 3. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest that are defined by tumor cell morphology and the presence or absence of CD8+ CCI cells	Pathologist, assisted by image analysis
Tumor infiltrating CD8+ lymphocytes	The number of CD8+ cells per unit area and the percent of counted cells that are scored as CD8+	Pathologist, assisted by image analysis
CCI		

CCI

CCI

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to avelumab, crizotinib or PF-06463922 and '**study treatment**' (or '**treatment group**') refers to one of the following.

Possible dose combinations for Group A (all dose combinations may not be explored):

- DL0: avelumab 10 mg/kg IV Q2W in combination with crizotinib 250 mg PO BID
- DL-1A: avelumab 5 mg/kg IV Q2W in combination with crizotinib 250 mg PO BID
- DL-1C: avelumab 10 mg/kg IV Q2W in combination with crizotinib 200 mg PO BID
- DL-1A-1C: avelumab 5 mg/kg IV Q2W in combination with crizotinib 200 mg PO BID
- DL-2C: avelumab 10 mg/kg IV Q2W in combination with crizotinib 250 mg PO QD
- DL-1A-2C: avelumab 5 mg/kg IV Q2W in combination with crizotinib 250 mg PO QD

Possible dose combinations for Group B (all dose combinations may not be explored):

- DL0: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 100 mg PO QD
- DL-1A: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 100 mg PO QD
- DL-1P: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 75 mg PO QD
- DL-1A-1P: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 75 mg PO QD
- DL-2P: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 50 mg PO QD
- DL-1A-2P: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 50 mg PO QD

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, physical measurements, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics

are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and Appendix 2, respectively.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

The full analysis set (FAS) will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first study treatment received.

4.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one study treatment, the patient will be classified according to the first study treatment received. In this non-randomized study, the FAS and the safety analysis set are identical.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

The DLT-evaluable set is the primary analysis set for the Phase 1b and will include all patients enrolled in Phase 1b who are in the safety analysis set, and either experience DLT during the first 2 cycles (28 days), or complete the observation period for the first 2 cycles of treatment.

A patient without DLT will be replaced if, for reasons other than drug-related toxicity,

a) the patient does not receive at least 75% of the planned doses of the first 2 cycles for crizotinib or PF-06463922, or

b) the patient does not receive at least 2 infusions of avelumab.

4.3.2. PK analysis sets

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or crizotinib or PF-06463922.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for avelumab, crizotinib or PF-06463922.

4.3.3. Biomarker analysis set

The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least 1 screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers:

CCI [redacted]

- Tumor IHC analysis set;

CCI [redacted]

4.3.4. Immunogenicity analysis set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one ADA/nAb sample collected for avelumab.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

Phase 1b:

There is no formal hypothesis testing in this phase. The objective of the dose-finding phase is to determine MTD or RP2D.

For Phase 1b of this study, due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI approach cannot be determined in advance.

Group A

For Group A, it is expected that approximately 12 to 36 patients will need to be enrolled in Phase 1b using the mTPI approach. At least 12 patients will be treated at the MTD in Phase 1b to further determine the RP2D according to the safety of the combination.

Group B

For Group B, it is expected that from approximately 12 to 36 patients will need to be treated in the dose-finding stage using the mTPI approach including at least 12 patients treated at the MTD. Up to 12 additional patients may be enrolled at the MTD (24 patients in total) to further characterize safety and tolerability and determine the RP2D.

Phase 2:

Group A

The sample size determination is based on Simon's Optimal Two-Stage design.

The first 12 patients treated at the RP2D during dose-finding stage in Phase 1b will be included as Stage 1 of Simon's Optimal Two-Stage design. If there are 3 or more patients with confirmed objective response in the first 12 patients treated at the RP2D, then an additional 33 patients will be enrolled and treated at that dose level.

The null hypothesis that the true ORR does not exceed 15% will be tested at the 1-sided significance level α=0.025 against the alternative:

H_0: ORR$\leq$15% versus H_a: ORR>15%

With 45 patients total, the study will have at least 80% power to reject the null hypothesis if the true ORR is $\geq$35%.

Group B

For Phase 2 of Group B, approximately 30 treatment-naïve patients will be enrolled. This will allow estimation of the ORR and CR rate with a maximum standard error of 0.091.

Table 4 provides the exact binomial 90% and 95% confidence intervals (CIs) for the ORR and CR rate based on different observed responses among 30 patients.

No formal hypothesis will be tested.

Table 4. Sample Size and Exact 90% and 95% CI for ORR and CR rate for Phase 2 of Group B

Sample Size	Number of Responders/ Complete Responders	ORR/CR Rate	90% CI	95% CI
30	6	20%	(9.1%, 35.7%)	(7.7%, 38.6%)
30	9	30%	(16.6%, 46.5%)	(14.7%, 49.4%)
30	12	40%	(25.0%, 56.6%)	(22.7%, 59.4%)
30	15	50%	(33.9%, 66.1%)	(31.3%, 68.7%)
30	18	60%	(43.4%, 75.0%)	(40.6%, 77.3%)
30	21	70%	(53.5%, 83.4%)	(50.6%, 85.3%)
30	24	80%	(64.3%, 90.9%)	(61.4%, 92.3%)
30	25	83.3%	(68.1%, 93.2%)	(65.3%, 94.4%)
30	26	86.7%	(72.0%, 95.3%)	(69.3%, 96.2%)
30	27	90%	(76.1%, 97.2%)	(73.5%, 97.9%)
30	28	93.3%	(80.5%, 98.8%)	(77.9%, 99.2%)
30	29	96.7%	(85.1%, 99.8%)	(82.8%, 99.9%)

5.1.2. Decision rules

Phase 1b:

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (pT) rate (pT = 0.30). If the toxicity rate of the currently used dose level

- is far smaller than pT, the mTPI will recommend escalating the dose level;
- if it is close to pT, the mTPI will recommend continuing at the current dose;
- if it is far greater than pT, the mTPI will recommend de-escalating the dose level.

These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose re-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a 2-way table. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules in the mTPI design are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically,

- the underdosing interval is defined as (0, pT-e1),
- the overdosing interval is defined as (pT+e2,1), and
- the proper-dosing interval is defined as (pT- e1, pT+ e2),

where e1 and e2 are small fractions.

Based on the safety profile of crizotinib and avelumab, e1 is selected as 0.05, and e2 is selected as 0.03. Therefore, the target interval for the DLT rate is (0.25, 0.33).

The 3 dosing intervals are associated with 3 different dose-escalation decisions:

- the underdosing interval corresponds to a dose re-escalation (RE),
- the overdosing interval corresponds to a dose de-escalation (D), and
- the proper dosing interval corresponds to staying at the current dose (S).

Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval.

The mTPI design calculates the UPMs for the 3 dosing intervals, and the 1 with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the underdosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Simulations have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

For both Group A and Group B, the Phase 1b dose finding evaluation is completed when 12 DLT-evaluable patients have been treated at the highest dose associated with a DLT rate ≤33% or, if the combinations are deemed too toxic, as determined by the DLT rate and/or lower than expected doses of the study treatments.

Phase 2:

Group A

The first 12 patients treated at the RP2D during dose-finding stage will be included as Stage 1 of Simon's Optimal Two-Stage design

- if there are ≥ 3 patients with confirmed OR out of 12 patients treated at the RP2D, then an additional 33 patients will be enrolled and treated at that dose level (Stage 2).
- if there are ≤ 2 patients with OR out of 12 patients treated at the RP2D and the remaining patients either discontinued or completed at least 12 months of treatment, then the study will not proceed to Stage 2 of Simon's Optimal Two-Stage design.

If the study proceeds into Phase 2, at the time of the primary analysis cutoff:

- if there are ≥ 12 patients with confirmed OR out of 45 patients treated at the RP2D, the null hypothesis will be rejected.
- if there are ≤ 11 patients with OR out of 45 patients treated at the RP2D, then it will be declared that the null hypothesis cannot be rejected.

Group B

There are no formal decision rules for Phase 2 of Group B.

5.2. General Methods

As described in Section 3.4, in this study '**treatment group**' is defined below.

Possible dose combinations for Group A (all dose combinations may not be explored):

- DL0: avelumab 10 mg/kg IV Q2W in combination with crizotinib 250 mg PO BID
- DL-1A: avelumab 5 mg/kg IV Q2W in combination with crizotinib 250 mg PO BID
- DL-1C: avelumab 10 mg/kg IV Q2W in combination with crizotinib 200 mg PO BID
- DL-1A-1C: avelumab 5 mg/kg IV Q2W in combination with crizotinib 200 mg PO BID
- DL-2C: avelumab 10 mg/kg IV Q2W in combination with crizotinib 250 mg PO QD
- DL-1A-2C: avelumab 5 mg/kg IV Q2W in combination with crizotinib 250 mg PO QD

Possible dose combinations for Group B (all dose combinations may not be explored):

- DL0: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 100 mg PO QD
- DL-1A: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 100 mg PO QD
- DL-1P: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 75 mg PO QD
- DL-1A-1P: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 75 mg PO QD
- DL-2P: avelumab 10 mg/kg IV Q2W in combination with PF-06463922 50 mg PO QD
- DL-1A-2P: avelumab 5 mg/kg IV Q2W in combination with PF-06463922 50 mg PO QD

Table 5 provides an overview of the summaries and the tabulations for this study taking into account the fact that at the time of this amendment only DL0 was studied (RP2D) and no other doses will be explored. Given the small number of patients (N=3 in Group B and N=0 in Group A since the pre-specified statistical criterion to proceed to Phase 2 was not met) who received study drug in Phase 2, summaries for Phase 2 alone will not be performed.

Table 5. Study Summaries and Tabulations

Summaries	Analysis Population	Phase 1b	Phase 1b and Phase 2 combined
Baseline characteristics and disposition	FAS	ND	Separately for Group A and Group B
DLTs	DLT-evaluable set	Group A and Group B separately	ND
Efficacy data	FAS	ND	Separately for Group A and Group B
Other safety data, exposure data, concomitant medications, non-drug treatment	Safety analysis set	ND	Separately for Group A and Group B
PK data for avelumab	PK analysis sets	ND	Separately for Group A and Group B
PK data for crizotinib	PK analysis sets	ND	Group A
PK data for PF-06463922	PK analysis sets	ND	Group B
Biomarker data	Biomarker analysis set	ND	Separately for Group A and Group B
Immunogenicity data	Immunogenicity analysis set	ND	Separately for Group A and Group B

ND: Not done.

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The ‘center’ factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 31 days prior to and including the date of first dose of study treatment.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

CCI

[redacted]

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date
- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

- Missing day: 1st day of the month and year of death
- Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.

- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY ;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b (Group A and Group B)

6.1.1.1. Primary analysis

The following analyses will be based on the DLT-evaluable set for patients in Phase 1b. DLTs will be listed and summarized by treatment group as described in Table 5.

6.1.2. Objective response as assessed by the Investigator per RECIST v1.1 (Group A and Group B)

6.1.2.1. Primary analysis

The following analyses will be based on the FAS by treatment group as described in Table 5. Assessment of response will be made using RECIST v1.1. Assessments below refer to investigator assessment.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD

- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set, and CR rate is the proportion of patients with CR in the analysis set.

For Group A, to account for the properties of the 2-stage Simon design, estimates of the response rates using uniform minimum variance unbiased estimator (UMVUE) will be provided (Porcher and Desseaux, 2012 [5]).

$$\hat{\pi} = \frac{S}{n_1} \quad if\ m = 1$$

$$\hat{\pi} = \frac{\sum_{x_1=(r_1+1)\cup(S-n_2)}^{S\cap n_1} {}^{n_1-1}C_{x_1-1}\ {}^{n_2}C_{S-x_1}}{\sum_{x_1=(r_1+1)\cup(S-n_2)}^{S\cap n_1} {}^{n_1}C_{x_1}\ {}^{n_2}C_{S-x_1}} \quad if\ m = 2$$

where m=1 is stopping stage 1 and m=2 is stopping stage 2, S=number of responses observed in stage 1 if m=1 and S=total number of responses observed if m=2, n_1= number of subjects in stage 1 and n_2 is the number of subjects in stage 2. The symbol ∩ implies minimum and the symbol implies maximum.

ORR will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method [2] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

For Group B, ORR and the CR rate will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method [2].

In addition, for both Group A and Group B, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), PD and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as ‘SD of insufficient duration’.

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS by treatment group as described in Table 5. Assessment of response will be made using RECIST v1.1. Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Disease control

Disease Control (DC) is defined as BOR of CR, PR, non-CR/non-PD or SD. DC rate (DCR) is the proportion of patients with DC.

DCR will be summarized by frequency counts and percentages.

6.2.2.3. Duration of response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 6.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Table 6. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 3, 6, 12, 18 and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 7 following the hierarchy shown.

Table 7. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The DR time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.2.4. Time to response

Time to response (TTR) is defined, for patients with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – date of first dose of study treatment +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.5. Progression-free survival

Progression-Free Survival (PFS) is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 16 weeks after the date of first dose of study treatment) in which case the death will be considered an event.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and at Week 8 (+1 week) and every 8 weeks (± 1 week) thereafter until PD regardless of initiation of subsequent anti-cancer therapy. The censoring and event date options to be considered for the PFS analysis are presented in Table 8.

PFS (months) = [date of event or censoring– date of first dose of study treatment +1]/30.4375

Table 8. Outcome and event dates for PFS analysis

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of first dose of study treatment [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - after 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after the date of first dose of study treatment the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rates at 3, 6, 9, 12, 18 and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to

Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 9 following the hierarchy shown.

Table 9. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment group. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median time of follow-up for PFS with 2-sided 95% CIs. In particular, the rates at 3, 6, 9, 12, 18 and 24 months will be estimated with corresponding 2-sided 95% CIs.

6.2.2.6. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose of study treatment to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 3, 6, 9, 12, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 9 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median time of follow-up for OS with 2-sided 95% CIs. In particular, the rates at 3, 6, 9, 12, 18, and 24 months will be estimated with corresponding 2-sided 95% CIs.

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group as described in Table 5.

C_{trough} and C_{max} for avelumab, crizotinib and PF-06463922 will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, cycle, and day. Dose-normalized parameters for avelumab, crizotinib and PF-06463922 (CDN-C_{trough} and CDN-C_{max}) will be reported as appropriate.

Other standard parameters including, but not limited to T_{max}, AUC_{last}, T_{last}, $AUC_{sd,\tau}$, $t_{1/2}$, CL, and V_z will be calculated for crizotinib and PF-06463922 as data permit.

Pharmacokinetic parameters for avelumab, crizotinib and PF-06463922 will be calculated from observed values or derived from plasma concentration-time data as described in Section 3.2.3.

Presentation of pharmacokinetic data will include:

- Linear-linear plots of mean and median plasma concentrations by nominal time for crizotinib and PF-06463922 will be presented for PK sampling days by treatment group, cycle, and study day. Similar plots will be presented for each individual patient concentrations. Patients who have undergone intrapatient dose reduction or escalation will be excluded from the median plasma concentration-time plots.
- Pharmacokinetic parameters for avelumab, crizotinib and PF-06463922 will be listed and summarized by treatment group/dose level, cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). For T_{max}, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. If an intrapatient dose escalation or reduction occurs, dose-dependent PK parameters (C_{trough}, C_{max} and AUC) for that patient may be dose-normalized when it is known that the drug exhibits linear PK within the dose range and other PK parameters will be reported as estimated; or may only be included in descriptive statistics and summary plots up to the time of the dose change. In addition, dose-normalized C_{trough}, C_{max} and AUC parameters will be summarized (as described above) using data pooled across treatment groups in which different crizotinib and PF-06463922 doses were administered.
- Box plots for C_{trough} and C_{max} for avelumab, crizotinib and PF-06463922 will be generated. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing changes in C_{trough}, C_{max} and AUC for each drug in individual patients will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots. In addition, box plots for dose-normalized avelumab C_{trough}, C_{max} , and AUC parameters will be created using data pooled across treatment groups in which different avelumab doses were administered.
- C_{trough} and C_{max} for avelumab will be plotted for each treatment group using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.
- Observed concentrations of avelumab, crizotinib and PF-06463922 from this study may be compared with the historical observed concentrations when each drug is administered alone.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any

association between avelumab, crizotinib and PF-06463922 exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

The following biomarker analyses will be based on the relevant biomarker analysis sets by treatment group as described in Table 5.

Descriptive summary statistics (mean, SD, median, Q1, Q3, coefficient of variation, minimum, and maximum), at each timepoint and ratio to baseline at each visit (if appropriate) will be provided for continuous biomarker variables, including CD8, CD68 and PD-L1 tumor analyses, as applicable. Non-continuous variables will be summarized using frequencies at each timepoint.

For each biomarker or set of biomarkers, patients may be classified as positive, negative, or some other category according to scoring algorithms and cut-offs established from external sources. If no external standards exist, biomarkers may be stratified using the median: ≤ median and > median, and by quartile. Percent of patients in each category will be tabulated.

Correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy may be assessed through statistical and graphical methods.

BOR will be summarized for each biomarker category if appropriate. The number of responders (patients with BOR of CR or PR) will be tabulated relative to biomarker classifications using a contingency table and a Fisher's exact test may be performed.

The relationship of the biomarkers (individually) at baseline with DR, PFS and OS may be explored using graphical methods such as box plots, as applicable.

6.2.6. Endpoints for immunogenicity data of avelumab

The following analyses of immunogenicity data will be based on the Immunogenicity analysis set by treatment group as described in Table 5.

Blood samples for avelumab immunogenicity testing will be collected as outlined in the "Schedule for Pharmacokinetic Sample Collection" table of the Schedule of Assessments section in the protocol.

Patients will be characterized into different ADA categories based on the criteria defined in Table 11.

Table 11. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative patients (titer < cutpoint)	Number of patients with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive patients (titer ≥ cutpoint)	Number of patients with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of patients with valid baseline ADA result
Treatment-boosted ADA	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab	Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the patient has at least one positive past-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response	If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response	If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable.

The number and percentage of patients in each ADA category will be summarized.

6.2.6.1. Time to and Duration of ADA response

The ADA analyses described below will include patients with treatment-induced ADA.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND patient is ongoing treatment with avelumab, or

- the last ADA assessment is positive AND patient discontinued treatment with avelumab AND the last planned ADA assessment is after the cut-off date.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of ADA response will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with ADA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

6.2.6.2. ADA titer

For patients who are ADA ever positive, the maximum observed ADA titer for a patient will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of patients having each discrete maximum titer value will be tabulated. The denominator to calculate the percentages will be the total number of patients in the associated ADA subcategory.

For patients with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

6.2.6.3. Analysis of PK and safety by immunogenicity status

The following ADA status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive

- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive

Data listings will include immunogenicity data together with relevant PK and safety data.

PK parameters and immunogenicity status

The following analyses will include patients in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoints pertinent to the immunogenicity analyses are C_{trough} and C_{max}. Blood samples for avelumab PK will be collected as outlined in the

"Schedule for Pharmacokinetic Sample Collection" table of the Schedule of Assessments section of the protocol.

C_{trough} and C_{max} will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time and ADA status. Linear-linear plots of mean and median for C_{trough} and C_{max} over nominal time and by ADA status will be presented.

Among patients with treatment-induced ADA, analyses will be conducted to assess whether C_{trough} and C_{max} have any changes before and after the first positive ADA assessment. To be included in this analysis, patients must have the same PK parameter available both before and after the first positive ADA assessment. Relative PK day will be calculated as:

(PK assessment nominal day) – (first positive ADA assessment nominal day).

Nominal day is the protocol scheduled timing for an assessment. For example, if C_{trough} is collected on Day 1 of Cycle 2 and the first positive ADA result is observed on Day 1 of Cycle 3, then the relative PK day for this C_{trough} is -28. Linear-linear plots of mean and median for C_{trough} and C_{max} over relative PK day will be presented.

Safety and immunogenicity status

The following analyses will include patients in the immunogenicity analysis set.

The frequency (number and percentage) of patients with each of the following will be presented by ADA status.

- TEAEs, by SOC and PT
- TEAEs leading to discontinuation of avelumab, by SOC and PT
- Grade ≥ 3 TEAEs, by SOC and PT
- SAEs, by SOC and PT
- IRRs, by PT

For patients who had at least one IRR and have treatment-induced ADA, time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be summarized taking into account whether the IRR occurred on or after the first ADA positive assessment or whether the IRR occurred before the first ADA positive assessment.

CCI [redacted]

CCI [redacted]

[redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI		

CCI

CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.4. Subset Analyses

The following subset analyses will be performed and presented separately for Group A and Group B (including Phase 1b and Phase 2 patients at the RP2D).

ORR and DR (if meaningful) will be summarized by prior anti-cancer therapy (Yes, No).

A listing of patients (along with their OR) whose ALK status determined centrally differs from their ALK status determined locally will also be presented.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS overall and separately by treatment group as described in Table 5.

6.5.1.1. Demographic characteristics

Demographic characteristics and physical measurements will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - Age (years): summary statistics
  - Age categories:

  - < 65 years, ≥ 65 years
  - < 65, 65-<75, 75-<85, ≥ 85 years
- Pooled Geographical Region (as applicable):
  - North America
  - Europe
  - Asia
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall treated population)
- Geographic Region (as applicable):
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2) and ECOG performance status.

In addition, the following summaries will also be presented, as applicable.

- ALK status from local versus central labs (yes, no, unknown)
- ROS1 gene translocation status from central labs
- c-MET gene amplification status
- c-MET exon 14 deletion status

A listing of the above data will also be presented.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis', 'Substance Use' and RECIST eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to date of first dose of study treatment (months), defined as (date of first dose of study treatment – date of initial diagnosis)/30.4375
- Time since diagnosis of locally advanced or metastatic disease (months), defined as (date of first dose of study treatment – date of diagnosis of locally advanced or metastatic disease)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No)
- Involved tumor sites at baseline

From the 'Substance Use' eCRF page:

- Smoking history (never smoker vs current vs former smoker)

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' and 'Substance Use' eCRF pages) and derived variables as above.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer therapy
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced - Metastatic
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drug therapies will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies
- Listing of anti-cancer radiotherapy
- Listing of anti-cancer surgeries

6.5.2. Study conduct and patient disposition

The following analyses will be performed based on the FAS overall and separately by treatment group as described in Table 5.

6.5.2.1. Patient disposition

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation

- Number and percentage of treated patients in each of the analysis sets defined in Section 4
- Number and percentage of patients with study drug ongoing (separately for each study drug)
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation
- Number and percentage of patients who entered long-term follow-up
- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation

In addition the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated patients by center.

In addition, a cross tabulation of patients who have discontinued/are ongoing treatment with avelumab vs patients who have discontinued/are ongoing treatment with crizotinib or PF-06463922 will also be provided.

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of the study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn
- Patients who receive the wrong treatment or an incorrect dose
- Patients who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set by treatment group as described in Table 5.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + 14 days – 1 day

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (eg, infusion cyclical, oral daily).

The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided for the following:

- Avelumab administered as a 1-hour IV infusion at a dose of 10 mg/kg or 5 mg/kg once every 2 weeks in 2-week cycles.
- Crizotinib administered orally BID as 250 mg or 200 mg or QD as 250 mg.
- PF-06463922 administered orally QD as 100 mg, 75 mg or 50 mg.

Analysis of exposure will be based on the calculated actual dose levels

- Avelumab - total dose / weight

- Crizotinib – total dose
- PF-06463922 – total dose

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 14 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab – first dose date of avelumab + 14)/7

Cumulative dose is the sum of the actual doses of avelumab received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/kg/2-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with avelumab (weeks)/2].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/2-week cycle) = [intended cumulative dose per cycle] / [intended number of 2-weeks in a cycle] = [d (mg/kg)] / [1 (2-week cycle)]

  = d (mg/kg/2-week cycle)

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]

  = 100 × [overall actual DI] / [d (mg/kg/2-week cycle)]

  where d = 5 or 10.

The summary of treatment exposure and compliance for avelumab will include the following information:

- Treatment duration (weeks)
- Total number of infusions received
- Cumulative dose (mg/kg)
- Dose intensity (mg/kg/cycle)
- Relative dose intensity (%).

6.5.3.2. Exposure to Crizotinib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with crizotinib (weeks) =(end date – date of first dose of crizotinib +1)/7,

where end date = date of last dose of crizotinib.

Duration of exposure to Crizotinib (weeks) =

(last dose date of crizotinib – first dose date of crizotinib + 1)/7

Cumulative dose is the sum of the actual doses of crizotinib received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

  = 100 × [overall cumulative dose] / [7 × d × duration of exposure to crizotinib in weeks]

  where d can be 500, 400, 250.

The summary of treatment exposure and compliance for crizotinib will include the following information:

- Treatment duration (weeks)
- Cumulative dose (mg)
- Dose intensity (mg/week)
- Relative dose intensity (%).

6.5.3.3. Exposure to PF-06463922

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with PF-06463922 (weeks) =(end date – date of first dose of PF-06463922 +1)/7,

where end date = date of last dose of PF-06463922.

Duration of exposure to PF-06463922 (weeks) =

(last dose date of PF-06463922 – first dose date of PF-06463922 + 1)/7

Cumulative dose is the sum of the actual doses of PF-06463922 received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of study drug to last dose of study drug]

  = 100 × [overall cumulative dose] / [7 × d × duration of exposure to PF-06463922 in weeks]

  where d can be 100, 75, 50.

The summary of treatment exposure and compliance for PF-06463922 will include the following information:

- Treatment duration (weeks)
- Cumulative dose (mg)
- Dose intensity (mg/week)
- Relative dose intensity (%).

6.5.3.4. Dose reductions

Dose reduction for avelumab is defined as actual non-zero dose < 90% of the planned dose.

Dose reduction for crizotinib and PF-06463922 is defined as a change to a non-zero dose level lower than that planned in the protocol.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.5. Dose interruptions

Applicable to crizotinib and PF-06463922.

An interruption is defined a 0 mg dose administered on one or more days for crizotinib and PF-06463922. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days, then it will be counted only once (example: If the actual dose on days 1-3 is 50 mg and actual dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1).
- If an interruption occurs for more than one day but the days are not consecutive, ie there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is 50 mg and actual dose on days 2 and 4 is 0 mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of patients with dose interruptions and the corresponding reasons will be summarized.

6.5.3.6. Dose delays

Applicable to avelumab.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – 14.

Dose delays will be grouped into the following categories:

- No delay
- 1-3 days delay
- 4-6 days delay
- 7 or more days delay

For example, for avelumab, administered on a 2-week schedule, if one patient receives avelumab on Day 1, then the next avelumab administration date will be on Day 15; however, if the patient receives avelumab on Days 16, 17 or 18, this is considered as 1-3 days delay.

No delay and 1-3 days delay will also be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, the worst case of delay if patients have multiple dose delays will be summarized.

6.5.3.7. Infusion rate reductions

Applicable to avelumab.

The number and percentage of patients with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the eCRF as well as the frequency of patients with 1, 2, 3 or ≥4 infusion rate reductions of ≥50% will be summarized.

6.5.3.8. Infusion interruptions

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set by treatment group as described in Table 5.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as

those started during the on-treatment period. **Prior medications** are medications, other than study drugs and pre-medications for study drug, which are started before the first dose of study treatment.

Prior and concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page. Pre-medications for study drug will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, summary of concomitant medications and summary of pre-medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the FAS by treatment group as described in Table 5.

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', and 'Follow-up Surgery' eCRF pages.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group as described in Table 5.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current studies data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current studies data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the

strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to interruption of avelumab
  - TEAEs leading to interruption of crizotinib
  - TEAEs leading to interruption of PF-06463922
  - TEAEs leading to discontinuation of avelumab
  - TEAEs leading to discontinuation of crizotinib
  - TEAEs leading to discontinuation of PF-06463922
  - TEAEs leading to discontinuation of any study drug
  - TEAEs leading to discontinuation of all study drugs
  - Related TEAEs leading to discontinuation of avelumab
  - Related TEAEs leading to discontinuation of crizotinib
  - Related TEAEs leading to discontinuation of PF-06463922
  - Related TEAEs leading to discontinuation of any study drug
  - Related TEAEs leading to discontinuation of all study drugs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death

  - irAEs
  - IRRs
- TEAEs by SOC and PT and worst grade
- TEAEs related to avelumab by SOC and PT and worst grade
- TEAEs related to crizotinib by SOC and PT and worst grade
- TEAEs related to PF-06463922 by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT
- TEAEs by SOC and PT: displaying in separate columns the All TEAEs / Related TEAEs / Grade ≥ 3 TEAEs / Related Grade ≥ 3 TEAEs

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to dose reduction of each study drug by treatment group:

- TEAEs leading to dose reduction of avelumab by SOC and PT
- TEAEs leading to dose reduction of crizotinib by SOC and PT
- TEAEs leading to dose reduction of PF-06463922 by SOC and PT

The listing of all AEs leading to dose reduction will also be provided with the relevant information.

6.6.1.3. Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.6). These IRRs will be considered as IRRs leading to interruption of infusion.
- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.6)

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of avelumab by SOC and PT
- TEAEs leading to interruption of crizotinib by SOC and PT
- TEAEs leading to interruption of PF-06463922 by SOC and PT

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

6.6.1.4. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- Related TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of crizotinib by SOC and PT
- Related TEAEs leading to discontinuation of crizotinib by SOC and PT
- TEAEs leading to discontinuation of PF-06463922 by SOC and PT
- Related TEAEs leading to discontinuation of PF-06463922 by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT
- Related TEAEs leading to discontinuation of any study drug by SOC and PT
- TEAEs leading to discontinuation of all study drugs by SOC and PT
- Related TEAEs leading to discontinuation of all study drugs by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity

- AE not related to study treatment
- Unknown
- Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs, by treatment group:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- irAEs leading to discontinuation of avelumab, by Cluster and PT
- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of patients with each of the following will be presented for IRRs, by treatment group:

- IRRs leading to death, by PT
- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- IRRs leading to discontinuation of avelumab, by PT
- Serious IRRs, by PT

- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later)

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq$ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq$ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade table will include number and percentage of patients with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.
- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of patients with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils

- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH)

6.6.5.2. Other laboratory parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (INR).
- Urinalysis: all urinalysis parameters
- Other parameters: hormone, and immunology parameters
- Pregnancy test.

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

6.6.6. Vital signs

Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate. Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF) and HR using individual (non-averaged) baseline assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

6.6.8. Physical examination

Number and percentage of patients with abnormal findings in physical examination will be summarized by body system.

6.6.9. ECOG performance status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by treatment group. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

1. Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38: 29-41, 1982.

2. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413, 1934.

3. Kalbfleisch JD, Prentice, RL. Statistical Analysis of Failure Time Data, 2nd Edition. Hoboken, Wiley Interscience, 2002.

4. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53: 457-81, 1958.

5. Porcher R, Desseaux K. What inference for two-stage phase II trials? BMC Med Res Methodol. 12:117, 2012.

9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 13. This case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

Table 13. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology) B) Histopathology / biopsy consistent with immune-mediated event Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	A) From the AE eCRF page Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify. B) From the AE eCRF page B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 14 and will be identified for IV drugs only.

Table 14. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs

Condition	Selection criterion
If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2	• AE onset date = date of infusion of study drug AND • AE timing related to study drug ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A	• AE onset date = date of infusion of study drug AND • AE timing related to study drug in ('DURING', 'AFTER')
4B	AE onset on the day after infusion