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

Compounds:	MSB0010718C, PF-02341066, PF-06463922
Compound Names:	Avelumab, Crizotinib, PF-06463922
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	2015-001879-43
Protocol Number:	B9991005
Phase:	1b/2

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	26 June 2015	Not applicable (N/A)
Amendment 1	10 August 2015	Per request from the US FDA, add statement that patients should have their tumors evaluated for EGFR mutations and have exhausted appropriate therapy, if positive. Corrected typographical errors within the protocol. Corrected an error on the SOA referring to PF-06463922 PK analysis that was added in error. Corrected an error for hematology and blood chemistry collection in the SOA (Both should occur on Cycles 1 and 2 on Days 1 and 8). Clarified efficiency of decision-rules based on mTPI design over traditional 3+3 design. Removed non-applicable text related to medical device safety reporting from the Serious Adverse Event section.
Amendment 2	24 March 2016	Revised Background, PF-06463922 Dose Modification and Electrocardiograms sections, Exclusion Criteria, and added a new Appendix to address any potential cardiac issues related to PF-06463922. Revised exclusion criteria to clarify requirement to stop prior 'cytotoxic'anti cancer therapy at least 2 weeks before study entry and provide for continuation of TKI therapy closer to study entry to mitigate risk of tumor flare. Clarified in the inclusion criteria (and indication section) that Group A patients should be previously treated in order to support the primary objective for this group. Modified inclusion criterion #9 regarding renal function to only include patients with estimated creatinine clearance >30 mL/min based on the known avelumab safety profile.

		Clarified modified Toxicity Probability Interval (mTPI) dose finding rules including Table 3, and removed previous Appendix 2 “Detailed Dose Escalation/De-Escalation Scheme for mTPI design” as the information was redundant. CCI [redacted] Revised procedure information, visit time window, and timepoints in the Schedule of Activities and Pharmacokinetic Sample Collection Table.Clarified that baseline signs and symptoms should be collected on the Medical History Case Report Form (CRF). CCI [redacted] Changed teratogenic risk of PF-06463922 from unknown to known in Section 4.3. Consolidated information for required Banked Biospecimens in Schedule of Assessment and Sections 7.4, 7.5, and 7.5.1. Removed requirement for antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA) and rheumatoid factor (RF) testing, as these are no longer required in avelumab protocols due to the lack of validity without a clinical correlate. Added screening HBV and HCV tests to the Schedule of Activities table to be consistent with Table 12. Revised frequency of adrenocorticotropic hormone (ACTH), Free thyroxine (FT4), and thyroid-stimulating hormone (TSH) assessments, based on emerging avelumab data and to be consistent with standard of care clinical practice.

		Removed requirement for 2 blood pressure readings to be taken 1 hour apart, as these assessments did not show blood pressure changes throughout the avelumab clinical trial program. Updated the Recommended Dose Modifications section to clarify that dose delays are only permitted up to 2 weeks, and rechallenging at the original dose after a reduction is only permitted on a case-by-case basis. Updated the Management of Avelumab + PF-06463922 Treatment-Related Toxicity guidelines. Combined Sections "Other Prohibited Concomitant Medications and Treatments" and "Other Prohibited Concomitant Medications and Therapies" as the information was overlapping. Included additional guidance for Group A. Additional guidance for use of inhibitors, inducers, and substrates of CYP3A enzymes for Group A in "Concomitant Medications" was provided. Corrected typographical errors and removed duplicate information within the protocol. Included additional information within the Background sections as well as additional references. Included additional abbreviations and removed inapplicable abbreviations.
Amendment 3	30 June 2017	The main rationale for the amendment is to include Group B Phase 2. Schedule of Assessments and Pharmacokinetic Sample Collection Table: CCI [redacted] Removed Follow-up Day 30 avelumab PK sample as it is no longer required. Other clarifications included. Objectives, Endpoints, Study Overview, Study Schema, Sample size calculation, and Efficacy Analyses revised for Group B Phase 2. Inclusion Criterion 2 revised to include requirement of no prior treatment for Group B

		Phase 2. Inclusion Criterion 6 corrected to state "0 to 2" vs "0 or 2". Exclusion Criterion 3 revised to not apply for Group B Phase 2. Exclusion Criterion 16 revised to update restrictons on cardiovascular disease to further protect patient safety in light of potential cardiac adverse events. Exclusion Criterion 19 updated to restrict listed conditions to within the past one year to align with current standards. Exclusion Criterion 22 clarified and Exclusion criteria 24 and 25 added due to emerging data on potential drug interactions with PF-06463922. Administration section for PF-06463922 revised due to emerging food effect data on PF-06463922, which allows for more flexibility in administration of PF-06463922. Updated Tables 6 and 7 for the management of treatment-related toxicities to harmonize the management of dose modification instructions witht the current avelumab Investigators Brochure. Added that PF-06463922 treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline. Revised Section 5.7.1.2 and Table 8 to remove maximum infusion time of 120 minutes as it has been determined that this restriction is not needed. Updated guidance for Inhibitors and Inducers of CYP Enzymes for Group B due to emerging data on potential drug interactions with PF-06463922 and to provide further instruction re: the types of concomitant medications allowed on study. Clarification added re: steroid use to specify the guidelines only apply if patient is still receiving avelumab. Table 12: Required Laboratory Tests revised to include corrections and remove redundant

		language. Clarification of ECG assessment and eliminated redundant language. Collection of Avelumab Pharmacokinetic Samples (Both Groups A and B) and Immunogenicity Assessment sections revised to provide better guidance on collection of avelumab PK and ADA samples, as well as proper sample management.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

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PROTOCOL SUMMARY

Indication:

For the avelumab/crizotinib combination (Group A): previously treated locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)–negative non-small cell lung cancer (NSCLC).

For the avelumab/PF-06463922 combination (Group B): locally advanced or metastatic ALK-positive NSCLC. Group B Phase 2 will be limited to patients who are treatment-naïve.

Background:

Non-small cell lung cancer is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative.[9,37] Standard therapy in later stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy[7,32] or immunotherapy.[5,28,30,31,42] Despite these advances, patients with NSCLC have a poor long-term survival.

Targeted therapy has been successful in NSCLC patients who have tumors that harbor various mutations, including EML4-ALK. The first approved agent for ALK-positive NSCLC is crizotinib. Although most patients with ALK-positive derive substantial clinical benefit from crizotinib, some ALK-positive NSCLC patients will not derive any benefit (intrinsic resistance) while other patients who initially derived benefit will develop resistance (acquired resistance). In the case of crizotinib-resistant ALK-positive NSCLC, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[6] In response to causes of crizotinib treatment failure, next generation ALK/ROS1 tyrosine kinase inhibitor (TKI)s are being developed. PF-06463922 is a selective, brain-penetrant ALK TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations.

Recent evidence has shown that tumors also require suppression of the host immune system for continued growth and spread. The development of agents targeting the interaction of programmed death receptor-1 (PD-1) and its ligands has shown promise in the treatment of various cancers including NSCLC.[5,11,31] Promising activity has been seen among patients with NSCLC that has progressed after platinum-based chemotherapy when using avelumab.[49]

It is becoming clear that combination strategies will be one way to enhance antitumor activity.[45] T cell suppression by immune checkpoint inhibitors may not be sufficient if not accompanied by T cell homing to tumor and their activation.[1,29] Zhou et al recently identified ALK in a screen as one of the genes involved in suppressing T cell infiltrating the tumor.[46] T cells transduced with pooled short hairpin RNA (shRNA) libraries targeting negative regulators of T cell function were injected into B16 melanoma-bearing mice. Short hairpin RNA-driven CD8+ T cell accumulation in tumors was found to be more than doubled relative to peripheral lymphoid tissue when ALK was targeted. These results suggest that the same immunostimulatory effect may be achieved with pharmacologic inhibition of ALK.

Indeed, preliminary internal Pfizer data demonstrates synergistic activity of both crizotinib and PF-06463922 with PD-L1 blockade in a murine ALK-negative colon carcinoma syngeneic model, CT26 (Pfizer, data on file).

Objectives and Endpoints:

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 Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 in previously treated locally advanced or metastatic ALK-negative NSCLC patients treated with the combination of avelumab and crizotinib at the RP2D;
- Group B: To assess ORR and complete response (CR) rate per RECIST v.1.1 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/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.

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[redacted]

Endpoints

Primary Endpoints

Phase 1b:

- First 2 cycles DLTs for Group A and Group B.

Phase 2:

- Confirmed Overall Response (OR) per RECIST v.1.1 for Group A.
- Confirmed OR and CR per RECIST v.1.1 for Group B.

Secondary Endpoints

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 4); vital signs (blood pressure, pulse rate);
- Disease Control (DC), Duration of Response (DR), Time to Tumor Response (TTR), Progression-Free Survival (PFS) per RECIST v.1.1, and Overall Survival (OS);
- Pharmacokinetic parameters of crizotinib, its metabolite PF-06260182, and avelumab will be determined as data permit:
    - Maximum plasma concentration (C_{max}), time to maximum plasma concentration (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, as data permit;
    - C_{max}, T_{max}, AUC_{tau}, metabolite to parent ratio for AUC_{tau} ($MRAUC_{tau}$), and metabolite to parent ratio for C_{max} (MRC_{max}) for PF-06260182 following multiple doses in the presence of avelumab;
    - C_{max}, T_{max}, AUC_{tau}, AUC_{last}, CL/F, and V_z/F for PF-06463922 following multiple dosing in the presence of avelumab, if data permit---;
    - Single and multiple dose pharmacokinetics (C_{max}, C_{trough} of avelumab in the presence of crizotinib and PF-06463922);
- Avelumab anti-drug antibodies (ADA; neutralizing antibodies);

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

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Study Overview:

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 Section 3; 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 as noted in Table 1 and Table 4. Determination of the MTD will be performed using the modified toxicity probability index (mTPI) design as described in Section 3.1.1.1.1 and Section 3.1.1.2.1 using dose de-escalation from the approved prescribed dose of crizotinib (250 mg BID), dose level established to be safe and effective for PF-06463922 (100 mg QD), 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, pharmacodynamics and antitumor activity of the combination.

Phase 2 (Group A)

After the MTD is identified and the RP2D is determined in Group A, the 12 patients treated at the RP2D will be considered Stage 1 of Simon's Optimal Two-Stage design. If 3 or more patients of the 12 in Phase 1b have a confirmed response per RECIST v.1.1, then in Phase 2 an additional 33 patients will be enrolled and treated. If there are fewer than 3 patients who have a confirmed objective response in the first 12 patients treated at the RP2D, 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 epidermal growth factor receptor (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 the Phase 2 portion to

further assess the antitumor activity, safety, pharmacokinetics and pharmacodynamics of the combination at the RP2D.

Study Procedures:

For detailed description of the study procedures, please consult the Schedule of Activities.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

		TREATMENT PERIOD (1 CYCLE = 14 DAYS)		END of TREATMENT/FOLLOW-UP		
		CYCLES 1-2	CYCLES ≥3			
Visit Identifier	**Screening (≤28 Days Prior to Enrollment)**	**Day 1**	**Day 1**	**End of Treatment / Withdrawal[25]**	**Follow-up Visits Day 30, 60, and 90 Days After Last Dose**	**Survival Follow-up[26]**
Visit Time Window		**(Cycle 2 ±3 days)**	**(±3 days)**	**(+3 days)**	**(±3 days)**	**(±3 days)**
Informed Consent	X					
Tumor History	X					
Medical/Oncology History (including prior regimens)	X					
Physical Examination	X	X	X	X		
Contraception Check[1]	X	X	X	X		
Ophthalmologic Examination (Group A only)[2]	X		X (Cycle 5 only)			
Baseline Signs and Symptoms[3]		X				
Weight	X	X	X	X		
Vital Signs[4]	X	X	X	X		
ECOG Performance Status[5]	X	X	X	X		
12-Lead ECG[6]	X	X	X (Cycle 3 only)	X		
Laboratory[7]						
Hematology[8]	X	X (Cycles 1 and 2 Days 1 and 8)	X	X	X	
Blood Chemistry[9]	X	X (Cycles 1 and 2 Days 1 and 8)	X	X	X	
Coagulation[10]	X	X	X	X		
ACTH, FT4, and TSH[11]	X[11]	X[11]	X[11]	X	X	
HBV, HCV	X[7]					

		TREATMENT PERIOD (1 CYCLE = 14 DAYS)		END of TREATMENT/FOLLOW-UP		
		CYCLES 1-2	CYCLES ≥3			
Visit Identifier	**Screening (≤28 Days Prior to Enrollment)**	**Day 1**	**Day 1**	**End of Treatment / Withdrawal[25]**	**Follow-up Visits Day 30, 60, and 90 Days After Last Dose**	**Survival Follow-up[26]**
Visit Time Window		**(Cycle 2 ±3 days)**	**(±3 days)**	**(+3 days)**	**(±3 days)**	**(±3 days)**
Urinalysis[12]	X			X	X	
Pregnancy Test[13]	X	X	X	X	X	
Registration and Treatment						
Registration[14]		X				
Avelumab Administration (Group A and Group B)[15]		X	X			
Crizotinib Administration (Group A) [15]		Orally on a continuous daily dosing schedule	→			
PF-06463922 Administration (Group B)[15]		Orally on a continuous daily dosing schedule	→			
Tumor Assessments						
CT or MRI Scan or equivalent[16]	X		X (Q8 weeks)	X		
Other Clinical Assessments						
Adverse Events[17]		→	→	X	X	
Concomitant and Subsequent Treatments[18]		→	→	X	X	
Survival Update						X
Other Samples						
Mandatory Archival formalin fixed paraffin embedded (FFPE) Tumor Tissue[19]	X					
[redacted] CCI	[redacted]		[redacted]	[redacted]		
[redacted] CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

		TREATMENT PERIOD (1 CYCLE = 14 DAYS)		END of TREATMENT/FOLLOW-UP		
		CYCLES 1-2	CYCLES ≥3			
Visit Identifier	**Screening (≤28 Days Prior to Enrollment)**	**Day 1**	**Day 1**	**End of Treatment / Withdrawal[25]**	**Follow-up Visits Day 30, 60, and 90 Days After Last Dose**	**Survival Follow-up[26]**
Visit Time Window		**(Cycle 2 ±3 days)**	**(±3 days)**	**(+3 days)**	**(±3 days)**	**(±3 days)**
[redacted] CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Blood for Avelumab PK[23] (Group A and Group B)		X	X (Up to Cycle 5, then Q12wks)	X		
Blood for Avelumab ADA and Neutralizing antibody (Immunogenicity) Testing[24] (Group A and Group B)		X	X (Up to Cycle 5, then Q12wks)	X	X 30 (±3) days after last avelumab dose	
Blood for Crizotinib PK[22](Group A)		X (Cycle 2 only)	X (Cycles 4 and 7)			
Blood for PF-06463922 PK[23] (Group B)		X (Cycle 2 only)	X (Cycles 4 and 7)			

Abbreviations: →= ongoing/continuous event; ADAs = anti-drug antibodies; AEs = adverse events; C = cycle; ECG = electrocardiogram, CT = computed tomography; MRI = magnetic resonance imaging; PK= pharmacokinetics

Footnotes

1. **Contraception Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
2. **Ophthalmologic Examination (Group A only)** (right and left eye): includes best corrected visual acuity (Snellen) and refractive error slit lamp biomicroscopy, and ophthalmoscopy and should be performed by an ophthalmologist. Testing will be performed at screening, on Cycle 5 Day 1, and should be repeated during the study whenever a vision disorder AE is observed or CTCAE grade change occurs from the previous visit.

3. **Baseline Signs and Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to study entry. Baseline signs and symptoms will be recorded on the Medical History case report form (CRF) page.
4. **Vital signs:** Blood pressure (BP) and pulse rate to be recorded in seated position. See Section 7.1.4.
5. **ECOG Performance Status:** Use Eastern Cooperative Oncology Group (ECOG) Performance Status– see Appendix 2.
6. **12-Lead ECG:** All patients require a single ECG measurement at screening. For triplicate ECGs, three (3) consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc. Triplicate ECGs should be performed immediately before PK blood draws at respective time points. On-treatment triplicate ECGs should be obtained at pre-dose and between 2 and 6 hours following both the morning crizotinib or PF-06463922 and avelumab dosing on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1. If the QTc is prolonged (>500 msec), then the ECG should be re-evaluated by a qualified person at the institution for confirmation (such as a cardiologist). On all other visits, single ECGs should be performed. Additional ECGs will be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events. See Section 7.1.5 for further details.
7. **Laboratory Tests:** Refer to Assessments Section 7.1.3 for Laboratory Tests list. On those weeks when no other assessments are required as per the SOA, a visit to the clinical site is not required unless the investigator considers it necessary.
8. **Hematology:** No need to repeat on Cycle 1 (C1D1) if screening assessment performed within 3 days prior to that date. See Assessments Section 7.1.3 for Laboratory Tests.
9. **Blood Chemistry:** Includes all tests marked as components of the Core Chemistry Test in Section 7.1.3. No need to repeat on Cycle 1 (C1D1) if screening assessment performed within 3 days prior to that date. Patients with liver metastases at baseline should have blood chemistry performed weekly during the first 6 weeks of study treatment.
10. **Coagulation:** No need to repeat on Cycle 1 (C1D1) if screening assessment performed within 7 days prior to that date. See Assessments Section 7.1.3 for Laboratory Tests list.
11. **ACTH, FT4, TSH Tests:** There is no need to repeat on Cycle 1 Day 1 if screening assessment is performed within 14 days prior to study enrollment.

    At screening, every 8 weeks, EOT visit, 30 days, 60 days and 90 days after last dose of study treatment and if clinically indicated.
12. **Urinalysis:** To be done at screening and EOT, and as clinically indicated. Dipstick is acceptable. Microscopic analyses should be performed if dipstick abnormal and/or if this is the local standard. No need to repeat on Cycle 1 Day 1 if screening assessment performed within 7 days prior to that date. In Korea, repeat exams should be completed at Day 1 of every cycle and at the end of treatment; all other countries should perform as clinically indicated, for example, upon diagnosis of renal cysts. Reflex Microscopy required if urine dipstick is positive for blood or protein. See Assessments Section Section 7.1.3 for Laboratory Tests.
13. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on two occasions prior to starting study therapy, once at the start of screening and once at the baseline visit immediately before investigational product administration. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study therapy during follow-up (up to 90 days after last study treatment), and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review board/ethics committee (IRB/ECs) or if required by local regulations. See Section 7.1.1.

14. **Registration**: Allocation of patients to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System (see Section 5.1).
15. **Study Treatment Administration**: **Group A and Group B:** Avelumab will be given as a 1-hour infusion every 2 weeks (as described in Section 5.4.1).
Group A: Crizotinib will be given orally BID (or QD based upon dose level) on a continuous daily dosing schedule (see Section 5.4.2).
Group B: PF-06463922 will be given orally QD on a continuous daily dosing schedule (as described in Section 5.4.3).
16. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is required to rule out CNS metastases. CT or MRI scans are to be done starting at Cycle 4/Week 8 (+1 week) then repeated every 4 cycles/8 weeks (±1 week). In case partial response (PR), complete response (CR) or progressive disease (PD) is observed according to RECIST v.1.1 CCI [redacted] confirmation CT or MRI should be performed no sooner than 4 weeks after the first documentation of response or disease progression. Tumor assessment should be repeated at the End of Treatment visit if more than 4 weeks have passed since the last evaluation. All radiographic images will be collected and may be objectively verified by a BICR independent third-party core imaging laboratory as described in the Imaging Manual. A bone scan (bone scintigraphy) or 18FDG-PET/CT is required at baseline, then every 16 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of CR confirmation for patients who have bone metastases. Tumor assessments should continue until documented disease progression regardless of initiation of subsequent anti-cancer therapy. See Section 7.6 for additional information.
17. **Adverse Event (AE) Assessments:** Adverse events should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (see Appendix 4). For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patients provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last dose of study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor (see Section 8.2). AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patients has taken at least 1 dose of study treatment through the patient's last visit. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
18. **Concomitant and Subsequent Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (at Days 30, 60, and 90 post-treatment ±3 days). All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
19. **Mandatory Archival FFPE Tumor Tissue**: A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections; archival tumor tissue collection should be within one year of start of study treatment, with no intervening systemic anti-cancer therapy (including neoadjuvant or adjuvant therapy). If an older archival tumor tissue (ie, > 1 year from start of study treatment) is available it can be submitted but will not fulfill the requirement for mandatory tumor tissue. If an FFPE tumor tissue block cannot be provided, sites should try to obtain 15 unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, a *de novo* (ie, fresh) tumor sample must be obtained (see footnote, De Novo Tumor biospsy) Acquisition of the mandatory tumor tissue may be completed prior to the 28-day screening window, but it is required for patient enrollment. Note that if archival FFPE

tumor tissue cannot be provided, FFPE tumor tissue from a *de novo* tumor biopsy performed at screening must be provided. Retrospective central testing will be performed to confirm ALK status as well as to test for alterations in ROS1, c-Met, and EGFR genes.

23. **PK Sampling**: Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic Samples Collection Table. Pharmacokinetic samples for avelumab will be collected from all patients in the study. Serial PK samples for crizotinib (**Group A**) and PF-06463922 (**Group B**) will be collected from all patients in the Phase 1b portion, and sparse sampling will be collected in all patients in the Phase 2 portion of the study.
24. **Blood for Avelumab Immunogenicity Testing (anti-avelumab antibodies; anti-drug antibodies [ADAs]) and Neutralizing Antibodies (Nab)**: All samples (3.5 mL) should be drawn within 2 hours before the start of the avelumab infusion. Additional samples for ADAs will be collected at 30 (±3) days after the end of avelumab therapy. If patient discontinues avelumab treatment and continues crizotinib or PF-06463922 monotherapy, the 30 day follow up sample is not required. All samples that are positive for ADA may also undergo characterization for Nab.
25. **End of Treatment**: Obtain these assessments if not completed within the prior week, except for tumor assessments, which need not be repeated if performed within the prior 4 weeks.
26. **Survival Follow-Up**: After discontinuation of study treatment, post-study survival status will be collected every 2 months until death or until 24 months after enrollment of the last patient, whichever occurs first. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.

Pharmacokinetic Sample Collection Table

Cycle Identifier	Cycle 1			Cycles -2								Cycles ≥3	Post-Treatment	
Study Day	Day 1		Day 8	Day 1							Day 8	Day 1	End of Treatment/ Withdrawal	Follow-up
Hours Post-Dose	0[a]	1		0[a]	1	2	4	6	8	24		0[a]		
PK Blood Samples for Avelumab[b] (Group A and Group B)	X	X	X	X	X						X	X[a] (Up to Cycle 5, then every 6 cycles thereafter)	X	
PK Blood Samples for Crizotinib[c] (Group A only)				X	X	X	X	X	X	X[c]		X[a] (Cycles 4 and 7)		
PK Blood Samples for PF-06463922[d] (Group B only)				X	X	X	X	X	X	X		X[a] (Cycles 4 and 7)		

PK = pharmacokinetic, ADAs=anti-drug antibodies

a. Pre-dose. For crizotinib or PF-06463922 PK samples, just prior to administration of crizotinib or PF-06463922. For avelumab PK sample, up to 2 hours prior to the start of infusion of avelumab.

b. One PK blood sample collected at each time point for avelumab. For patients in Group A and B, blood samples for avelumab PK will be collected (3.5 mL) at pre-dose and 1 hour from the start of infusion (end of infusion) on Day 1, and anytime during the Day 8 clinic visit of Cycles 1 and 2. Pre-dose samples will be collected on Day 1 of Cycles 3 through 5 followed by Day 1 every 6 cycles thereafter. An additional sample will be collected at the End of Treatment.

c. **Group A only**: One PK blood sample (3 mL) collected at each time point for crizotinib. For all patients enrolled in Phase 1b of Group A, serial blood samples for PK of crizotinib will be collected at: pre-dose, 1, 2, 4, 6 and 8 hours post-dose on Day 1 of Cycle 2 only. Only for patients at DL-2C or DL-1A-2C, an additional 24 hour sample (prior to Day 2 dose of crizotinib) post Day 1 of Cycle 2 dose will be obtained. Sparse blood samples (pre-dose only) will be collected on Day 1 of Cycles 4 and 7. For all patients enrolled in Phase 2, only pre-dose blood samples will be collected on Day 1 of Cycles 2, 4, and 7 for PK of crizotinib.

d. **Group B only**: One PK blood sample collected (4 mL) at each time point for PF-06463922. For all patients enrolled in Phase 1b of Group B, serial blood samples for PK of PF-06463922 will be collected at: pre-dose, 1, 2, 4, 6, 8, and 24 hours (prior to Day 2 PF-06463922 dose) post-dose on Day 1 of Cycle 2 only. Sparse blood samples (pre-dose only) will be collected on Day 1 of Cycles 4 and 7. For all patients enrolled in Phase 2, only pre-dose blood samples will be collected on Day 1 of Cycles 2, 4, and 7 for PK of PF-06463922.

1. INTRODUCTION

1.1. Indication

For the avelumab/crizotinib combination (**Group A**): previously treated locally advanced or metastatic Anaplastic Lymphoma Kinase (ALK)–negative -NSCLC.

For the avelumab/PF-06463922 combination (**Group B**): locally advanced or metastatic ALK-positive NSCLC. Group B Phase 2 will be limited to patients who are treatment-naïve. Following the identification of the MTD and determination of the RP2D, approximately 30 additional patients who are treatment-naive will be enrolled in the Phase 2 portion to further assess the antitumor activity, safety, pharmacokinetics and pharmacodynamics of the combination at the RP2D.

1.2. Background and Rationale

1.2.1. Non-Small Cell Lung Cancer

NSCLC is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative.[9,37] Standard therapy in later stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy or immunotherapy.[5,28,30,31,42] Targeted therapies such as TKIs may be used for appropriate patients. In spite of these treatments, 5-year survival is only about 17.0% for advanced-stage NSCLC patients, highlighting the need for novel therapies and treatment regimens.[7,32]

1.2.1.1. ALK Alterations in NSCLC

A rearrangement within chromosome 2p resulting in the formation of a fusion gene product comprising portions of the echinoderm microtubule-associated protein-like-4 (EML4) gene and the ALK gene was discovered in 2007 in NSCLC cell lines and archived clinical specimens.[40] A subsequent series of studies have described 9 fusion variants of EML4-ALK plus additional but less common fusion partners with ALK.[23] Currently, there are at least 27 different ALK fusion variants reported in the literature, the majority of isoforms involve EML4-ALK. ALK-positive NSCLC patients, who represent between 3% and 5% of all NSCLC cases, tend to be young (average age 50 years at diagnosis), and light or never smokers.[27] Oncogenic fusions of ALK and ROS1 define two distinct subsets of human lung adenocarcinoma patients and play essential roles in regulation of tumor cell survival, growth, and metastasis.

Crizotinib, a potent and selective adenosine triphosphate (ATP) competitive inhibitor of ALK, ROS 1, RON, and c-MET receptor tyrosine kinases and relevant oncogenic variants, was first studied clinically in ALK-positive NSCLC in an ongoing Phase 1 trial soon after the discovery of the EML4-ALK fusion protein oncogenic driver potential in NSCLC.[40] The clinical benefit of crizotinib led to the US approval of crizotinib (XALKORI®) in August 2011 for the treatment of advanced ALK-positive NSCLC patients (See Section 1.2.2.2).

Although most patients with ALK-positive tumors derive substantial clinical benefit from crizotinib, some patients will not derive any benefit (intrinsic resistance) while other patients who initially derived benefit will develop resistance (acquired resistance). In the case of crizotinib-resistant ALK-positive NSCLC, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[6]

Resistance to ALK TKIs may be related to gatekeeper mutations along with activation of bypass resistance mechanisms such as germline variations in tumor response pathways. Multiple types of ALK kinase domain have been identified in crizotinib-refractory patients.[6,8,21,44] Additional mechanisms of resistance include mutations in the ALK kinase domain, development of bypass mechanisms in the presence of ALK TKI sensitivity that is crizotinib-suppressed, failure of drug delivery to the target (such as the central nervous system [CNS]), ALK fusion gene amplification, and development of EGFR signaling.[6,8,44] In response to these causes of crizotinib treatment failure, next generation ALK/ROS1 TKIs are being developed.

PF-06463922 is a selective, brain-penetrant TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations. Activity has been seen in previously treated patients with ALK and ROS1 fusion genes (ORR 44% [95% CI 27 – 62]), including intracranial responses.[50] (See Section 1.2.2.2).

1.2.1.1.1. Potential activity of ALK TKIs in ALK-negative NSCLC

Recently, ALK was identified in a screen as one of the genes involved in suppressing T cell infiltrating the tumor.[46] Short hairpin RNA-driven CD8+ T cell accumulation in tumors was found more than doubled relative to peripheral lymphoid tissue when ALK was targeted. These results suggest that the same immunostimulatory effect may be achieved with pharmacologic inhibition of ALK.

Preliminary internal Pfizer data demonstrates synergistic activity of both crizotinib and PF-06463922 with PD-L1 blockade in a murine ALK-negative colon carcinoma syngeneic model, CT26 (Pfizer, data on file). More information regarding the background and purpose of studying avelumab with crizotinib in ALK-negative patients is found in Section 1.2.3.

1.2.1.2. Activity of Immune Checkpoint Inhibitors in NSCLC

Recent evidence has shown that tumors require suppression of the host immune system for continued growth and spread. The development of agents targeting the interaction of PD-1 and its ligands has shown promise in the treatment of various cancers including NSCLC.[5,11,31] Substantial clinical activity was observed with anti-PD-1 antibodies, nivolumab and pembrolizumab, with ORRs of 15% and 20%, respectively, and long duration of response (DR) in heavily pretreated unselected NSCLC patients.[4,5,10] Similarly impressive activity was observed in the first-line treatment setting with ORRs of 30% and 26% for nivolumab and pembrolizumab, respectively.[12,33] Anti-PD-L1 antibodies have also been studied in pre-treated unselected NSCLC with response rates of 16% to 23% for MEDI4736 and MPDL3280a, respectively.[3,15]

The initial study of nivolumab in NSCLC reported responses in patients with ALK-positive NSCLC; these results are difficult to interpret as the ORR was associated with wide confidence intervals.[3,15] There were only 7 patients with ALK-positive NSCLC in the Phase 3 CheckMate-057 non-squamous NSCLC trial (N=582 for the study), 4 received nivolumab and 3 received docetaxel. ORR, OS, and PFS interpretation could not be performed due to the small subset of patients.[31] It has been suggested that the use of combination therapy of immune checkpoint inhibitors with other agents would be more effective in stimulating immune responses.[51]

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

Avelumab (MSB0010718C) is a fully human IgG_1 monoclonal antibody directed against the Programmed Death Ligand-1 (PD-L1) molecule that is expressed by tumor cells, as well as by a number of immune cells. Avelumab has a calculated molecular weight of 143,832 Dalton.

Compared with anti-PD-1 antibodies that target T cells, avelumab targets tumor cells. Avelumab is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2/PD-1 pathway intact to promote peripheral self-tolerance.[24] For complete details of the in vitro and preclinical studies, refer to avelumab Investigator's Brochure (IB).[17]

Avelumab is being developed jointly by Pfizer and Merck KGaA. The clinical development program for avelumab currently includes 4 ongoing studies in patients with various solid tumors conducted by Merck KGaA (EMR 100070-001, EMR 100070-002, EMR 100070-003, and EMR 100070-004).

Trial EMR100070-001 is a Phase 1, open-label, multiple-ascending dose clinical study aimed to investigate the safety, tolerability, PK, biological, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. This trial consisted of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor indications. Avelumab was administered intravenously at the assigned dose level as a 1-hour intravenous (IV) infusion once every 2 weeks. The following dose levels (DLs) were investigated: 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg.

As of 05 November 2014, a total of 50 patients were treated in the dose escalation phase of the trial, with 4, 13, 13, and 20 patients being treated with avelumab of 1, 3, 10, and 20 mg/kg, respectively. None of the patients treated with doses up to 10 mg/kg experienced a DLT, and the 10 mg/kg dose of avelumab was considered a safe and well-tolerated dose for further investigation in the dose expansion cohorts. One DLT (a Grade 3 immune-related AE characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

A total of 11 expansion cohorts are ongoing and 480 patients have been enrolled and treated by the cutoff date with the recommended dose of 10 mg/kg avelumab once every 2 weeks.

Of the 480 patients treated in the pooled expansion cohorts, 218 (45.4%) experienced at least 1 Grade ≥3 treatment-emergent adverse event (TEAE), and 330 (68.8%) reported treatment-related TEAEs, of which 59 (12.3%) reported Grade ≥3 treatment-related TEAEs.

The most frequently reported (incidence ≥5%) treatment-related TEAEs (any grade) in the pooled expansion cohort are summarized in the avelumab IB.[17] The most frequently reported (occurring in at least 2 patients) Grade ≥3 treatment-related TEAEs in the pooled expansion cohorts are presented in avelumab IB.[17]

Overall, 176 of the 480 patients (36.7%) treated in the dose expansion cohorts had serious TEAEs. Of these, 22 (4.6%) patients experienced dyspnea, 19 patients (4.0%) disease progression, 12 patients (2.5%) pleural effusion, 11 patients (2.3%) pneumonia, 8 patients respiratory failure (1.7%) and 7 patients (1.5%) anemia. All other serious TEAEs were each reported in less than 1.5% of patients. Of the serious TEAEs considered treatment-related by the Investigator (31 patients; 6.5%), the following were reported for 2 or more patients: infusion-related reaction (4 patients, 0.8%), pneumonitis (3 patients, 0.6%), and disease progression, dyspnea, and hypercalcemia (2 patients each, 0.4%).

As of 05 November 2014, deaths were reported in 134 (27.9%) patients. The primary cause of death was attributed to disease progression in 101 (21.0%) patients. Seven treatment-related AEs with fatal outcome were reported. Causes of the additional deaths were listed as due to AEs unrelated to study treatment, "other," and "unknown". Of the 137 patients who died, 53 patients (11.0%) died within 30 days of the last administration of trial treatment. The 7 deaths due to TEAEs related to trial treatment were attributed to the following events: pneumonitis radiation-induced and dyspnea; acute liver failure associated with autoimmune hepatitis (no biopsy/autopsy performed); disease progression; fatal anoxic brain injury (not related) after cardiac arrest (related); autoimmune hepatitis with hepatic failure and fatigue (no biopsy/autopsy performed); respiratory distress and sepsis; and acute respiratory failure, acute exacerbation chronic obstructive pulmonary disease (COPD), and leukocytosis (occurred after the end of the on-treatment period).

A total of 80 patients (16.7%) treated in the dose expansion cohorts withdrew permanently from trial treatment due to TEAEs. In 34 (7.1%) of these patients, the TEAEs leading to trial treatment discontinuation were considered related to trial treatment by the Investigator. The most frequent (≥2 patients) TEAEs leading to trial treatment discontinuation were infusion-related reaction (8 withdrawals; 1.7%), GGT increased and rash (3 withdrawals each, 0.6%), and aspartate aminotransferase increased, blood creatine phosphokinase increased, and disease progression (2 withdrawals each, 0.4%).

Immune-related Adverse Events: As of 05 November 2014, a cumulative review identified 56 patients with potential immune-related AEs (irAEs) out of 480 patients (11.7%) treated in the dose expansion part of trial EMR 100070-001, and 4 cases out of 50 patients (8.0%) treated in the dose escalation part of trial EMR 100070-001, for a total of 69 irAEs. Of these 69 irAEs, 46 (67%) were assessed as treatment-related by the Investigator, and 23 (33.3%) were assessed as not treatment-related by the Investigator. Twenty-six irAEs were assessed as Grade 1, 29 as Grade 2, 11 as Grade 3, 2 as Grade 4, and 1 had a fatal outcome (radiation pneumonitis) (note: 2 Grade 3 suspected autoimmune hepatitis, not confirmed by biopsy, also had a fatal outcome).

Infusion-Related Reactions: Two suspected unexpected serious adverse reactions (SUSARs; anaphylactic reaction and infusion-related reaction) involving 2 patients were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions and hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions and hypersensitivity have been classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of a histamine H1 receptor (H1) blocker plus acetaminophen/paracetamol was implemented for all trial patients starting 29 January 2014.

As of 05 November 2014, overall 49 (10.2%) of the 480 patients in the expansion cohort experienced at least 1 episode of infusion-related reaction when receiving avelumab monotherapy. Most of the events were Grade 1 (8 patients, 1.7%) or Grade 2 (36 patients, 7.5%) in severity, while Grade 3 (3 patients, 0.6%) and Grade 4 events (2 patients, 0.4%) were less frequent. No Grade 5 events were reported. Most of the infusion-related reaction events had an onset after the first (30 patients, 6.3%) or second (16 patients, 3.3%) avelumab infusion. In 8 patients (1.7%), avelumab treatment was permanently discontinued because of infusion-related reaction events. In addition, 1 patient (2.0%) in the dose escalation cohort also experienced an infusion-related reaction event (Grade 2).

Mandatory premedication with H1 blockers plus acetaminophen/paracetamol was implemented for all patients who receive avelumab. This premedication procedure was applied to 28/50 and 440/480 patients in the dose escalation and the pooled treatment expansion cohort, respectively. Under this premedication procedure, 33 of 440 patients (7.5%) in the expansion cohort experienced infusion-related reaction events, with 6 patients (1.4%) having Grade 1, 26 patients (5.9%) having Grade 2, and 1 patient (0.2%) having Grade 3 events. No infusion-related reaction events were reported in the 28 patients premedicated and treated in the dose escalation cohort.

In addition to the aforementioned patients, 1 case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The patient died due to anoxic brain injury 7 days later; no autopsy was performed.

The management of infusion-related reactions and severe hypersensitivity reactions can be found in Section 0 and Section 5.6.1.3, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf.

Avelumab PK and dose proportionality following the first 1-hour infusion have been characterized in 57 Caucasian patients treated in the dose escalation and expansion cohorts of Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of C_{max} and AUC_{tau} increased in a dose proportionate fashion across the 1, 3, 10, and 20 mg/kg doses. Apparent half-life tended to increase with dose, likely due to target mediated disposition at lower doses, but terminal half-life of 10 and 20 mg/kg doses were similar (106-134 hours). This likely indicates target mediated elimination does not increase at these two doses and target occupancy is very high.

Target occupancy (TO) on peripheral blood CD3+ T-cells was investigated in human blood in vitro by flow cytometry after spiking of whole blood samples from 8 healthy volunteers with avelumab over a concentration of 0.003-10 μg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 μg/mL ±0.042 μg/mL with a plateau indicating at least 95% receptor occupancy reached in all blood samples at 1 μg/mL. PK profiles obtained from the dose escalation phase of Trial EMR 100070-001 found all patients at 10 mg/kg dose reached or exceeded the serum level (median C_{trough} 20-37 ug/ml) of avelumab required for >95% TO. For patients treated with 3 mg/kg of avelumab, 10 of 13 patients reached the required serum level (3.7-8.3 ug/ml).

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[17]

1.2.2.1.1. Activity of Avelumab in NSCLC

The clinical efficacy of avelumab in NSCLC is based on data from the unselected NSCLC expansion cohort in the ongoing Phase 1 trial EMR 100070-001 using a data cutoff date of 15 January 2015, 13 weeks after the start of avelumab treatment of the last patient in this expansion cohort (a total of 184 treated patients). This group of NSCLC patients presented with a median age of 65 years with Stage IIIB or IV NSCLC that had progressed after at least 1 line of platinum-containing doublet chemotherapy for locally advanced or metastatic disease. The ECOG PS was 0 in 30% of patients and 1 in 70% of the patients. The histologies treated were adenocarcinoma (62%), squamous cell carcinoma (29%), or other (9%). These patients received avelumab 10 mg/kg Q2weeks. Promising activity has been seen among patients with NSCLC that has progressed after platinum-based chemotherapy when using avelumab.[17] The median duration of treatment was 12.2 weeks (range 2.0-64.0). As of the date of data cutoff, 41 of the 184 patients remained on treatment. The ORR for the NSCLC expansion cohort was 13.6% (95% CI: 9.0 -19.4) including confirmed and unconfirmed responses. One patient (0.5%) had a CR while 24 patients had confirmed and unconfirmed PR (13.0%). The disease control rate (DCR), patients with confirmed and unconfirmed CR, PR, and SD, was 50.5%. The median PFS in the NSCLC expansion cohort was 11.6 weeks (95% CI: 8.4 – 13.7) with the proportion of patients alive and progression-free at 24 weeks and 48 weeks equal to 26.2% (95% CI: 19.9 – 33.0) and 18.1% (95% CI: 12.0 – 25.2), respectively. The median OS in the NSCLC expansion cohort was 8.4 months (95% CI: 7.3 – 10.7) with 37.0% of patients alive at 12 months (95% CI: 27.1-46.9) in this heavily pretreated group of patients. The toxicity profile of avelumab was noted to be in line with other immune checkpoint inhibitors of PD-1 and PD-L1[17]

1.2.2.2. Crizotinib (Xalkori® PF-02341066)

Crizotinib is a selective ATP competitive small molecule inhibitor of ALK, ROS1, RON, and c-MET/Hepatocyte Growth Factor Receptor (HGFR) tyrosine kinases and their oncogenic variants (eg, ALK or ROS1 fusion proteins or c-MET/HGFR mutant variants). Consistent with this mechanism of action, crizotinib inhibited phosphorylation of c-Met/HGFR and selected ALK fusion or mutant variants in tumor cells both in vitro and in vivo, and RON and ROS1 in vitro. Crizotinib exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion or selected mutations involving the ALK gene locus (EML4-ALK or nucleophosmin- [NPM] ALK fusion variants).

The PK of crizotinib is explained in detail in the crizotinib IB.[18] Oral dosing of crizotinib at 250 mg BID showed plasma concentrations to reach steady state within 15 days. The mean apparent terminal half-life was 42 hours in cancer patients after a single dose. Crizotinib is absorbed with a peak plasma concentration occurring between 4 and 6 hours under fasted condition. Crizotinib is a substrate of P-glycoprotein and is predominately metabolized by CYP3A4/5. Crizotinib inhibited P-glycoprotein (P-gp), hepatic uptake transporter, organic cation transporter 1 (OCT1), and renal uptake transporter, organic cation transporter 2 (OCT2) *in vitro* at clinically relevant concentrations. Elimination of crizotinib was related to its hepatic, and possibly gastrointestinal, metabolism with a mean of 63.1% of [^{14}C] crizotinib excreted in the feces and 22.2% in the urine.[18]

Overall, the AEs reported for crizotinib in clinical studies were considered generally tolerable and manageable. For single-agent crizotinib use, the most common AEs (≥20% of patients) reported from 1511 patients with advanced NSCLC regardless of causality were vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, and decreased appetite. The majority of AEs were Grades 1 or 2 in severity, as treatment-related AEs of Grades 3, 4, or 5 in severity were observed among 547 (36.3%) advanced NSCLC patients who received at least 1 dose of single-agent crizotinib250 mg BID. The most common Grade 3 treatment-related AEs were neutropenia, elevated transaminases, hypophosphatemia, fatigue, leukopenia, lymphopenia, nausea, vomiting, electrocardiogram QT prolonged, and edema. The most common Grade 4 treatment-related AEs were neutropenia, elevated transaminases, hepatotoxicity, interstitial lung disease (ILD), and abdominal pain. The Grade 5 treatment-related AEs that occurred most commonly were ILD (5 patients; 0.3%), death (4 patients; 0.3%), pneumonia (2 patients; 0.1%), hepatotoxicity (2 patients; 0.1%), lung infection (2 patients; 0.1%), disseminated intravascular coagulation (1 patient; 0.1%), arrhythmia (1 patient; 0.1%), dyspnea (1 patient; 0.1%), and pulmonary embolism (1 patient; 0.1%).[18]

There are special warnings regarding crizotinib use that must be considered and are described in detail in the crizotinib IB.[18] Drug-induced hepatotoxicity occurred in less than 1% of all patients treated with crizotinib and usually appeared within the first 2 months of therapy. Other warnings are pneumonitis/ILD and QTc prolongation which both occurred in fewer than 2% of patients and bradycardia which occurred in approximately 6% of patients. Specific management for these events is noted in Table 6.

Clinical trials using crizotinib showed high rates of objective tumor response that were rapid and durable in Studies A8081001 and A8081005. In Study A8081007 (PROFILE 1007), second-line treatment of advanced ALK-positive NSCLC patients (after initial platinum-based chemotherapy) with crizotinib demonstrated a significant improvement in median PFS when compared to chemotherapy (pemetrexed or docetaxel monotherapy, median PFS: 7.7 months vs. 3.0 months, respectively; HR 0.487; 95% CI: 0.371, 0.638; P <0.001). The objective response rates (ORRs) were 65% (95% confidence interval (CI), 58, 72%) with crizotinib, as compared with 20% (95% CI:14, 26%) with chemotherapy (P<0.001) The duration of response (DR) was 32.1 weeks with crizotinib (95% CI 2.1, 72.4 weeks), as compared to 24.4 weeks with chemotherapy (95% CI 3.0, 43.6 weeks).[52] Validated questionnaires (EORTC QLQ-C30 and QLQ-LC13) showed a significantly greater

improvement in patient-reported lung cancer symptoms and global quality of life receiving crizotinib as compared with chemotherapy.[52] The first-line use of crizotinib was evaluated in Study A8081014 (PROFILE 1014) as compared with chemotherapy. The treatment of ALK-positive NSCLC with crizotinib demonstrated significant improvement in median PFS and ORR when compared with pemetrexed plus platinum chemotherapy (median PFS: 10.9 months vs. 7.0 months, respectively; HR 0.454; 95% CI: 0.346 -0.596; P <0.001; ORR: 74% vs. 45%, respectively; P <0.001). The DR was 11.3 months with crizotinib (95% CI 8.1, 13.8), as compared with 5.3 months (95% CI 4.1, 5.8).[41]

Additional improvements were seen in the use of crizotinib over chemotherapy in patients with ROS1 fusion protein-related NSCLC.[36]

Complete information may be found in the crizotinib IB, which is also to be considered the single reference safety document (SRSD) for crizotinib.[18]

1.2.2.3. PF-06463922

PF-06463922 is a selective, ATP competitive small molecule inhibitor of the ALK and ROS1 receptor tyrosine kinases (RTK) that preclinically also potently inhibits ALK kinase domain mutations responsible for ALK TKI resistance.

In vitro, PF-06463922 demonstrated potent, concentration-dependent inhibition in catalytic activities of ALK, ALK mutants and ROS1 kinases in recombinant enzyme and cell based assays. PF-06463922 also inhibited ALK- and ROS1-dependent oncogenic functions in human NSCLC cell lines, and demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting either non-mutant ALK and ROS1 fusion variants or mutant ALK fusions that are acquired and resistant to crizotinib treatment.

In vivo, PF-06463922 demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib resistant EML4-ALK^{L1196M} or EML4-ALK^{G1269A} mutations. PF-06463922 treatment considerably reduced the tumor size and prolonged animal survival in the orthotopic brain models (EML4-ALK and EML4-ALK^{L1196M} in mice. The anti-tumor efficacy of PF-06463922 was dose dependent and demonstrated strong correlations to inhibition of ALK or ROS1 phosphorylation.

As of 24 April 2015, preliminary single-dose PK of PF-06463922 has been evaluated in 20 patients in doses ranging from 10-200 mg QD in the B7461001 dose-escalation study. After a single oral dose in the fasted state, peak plasma concentrations (C_{max}) of PF-06463922 were achieved at a median time (T_{max}) ranging from 1.25-2.0 hours across the different doses. Across the doses, mean C_{max} and AUC_{inf} values for PF-06463922 ranged from 50.8 to 1201 ng/mL and from 900 to 21429 ng•hr/mL, respectively, and increased in a relatively dose-proportionate manner. Mean estimates of terminal half-life in this study ranged from 18.8 to 26.3 hours. Preliminary steady-state PK of PF-06463922 has been evaluated in 26 patients following repeated doses ranging from 10-200 mg QD in the B7461001 dose-escalation study. After multiple doses of PF-06463922 in the fasted state,

peak plasma concentrations (C_{max}) of PF-06463922 were achieved at a median time (T_{max}) ranging from 1.0-2.0 hours across the different doses. Across the doses, mean C_{max} and AUC_{τ} values for PF-06463922 ranged from 60.3 to 1043 ng/mL and from 713 to 8057 ng•hr/mL, respectively. While steady state AUC values at doses greater than 100 mg QD seem to increase at a less than dose proportional manner, at the time of this analysis, the number of patients enrolled at higher doses was small and a definitive conclusion regarding dose linearity cannot be made. Furthermore, doses above 100 mg of PF-06463922 are not planned for this study. Mean estimates of effective half-life in this study ranged from 11.8 to 23.4 hours.

A Phase 1 monotherapy study of PF-06463922 in patients with ALK-positive and ROS1-positive advanced NSCLC (B7461001; NCT01970865) is currently ongoing. As of the data cutoff date of 20 April 2015, 44 patients were evaluable for safety across all dose levels tested. As of 25 March 2015, 12 patients were treated at 100 mg QD PF-06463922 for at least 4 weeks. No DLTs occurred at this dose level and the safety profile was tolerable. One DLT was noted among three patients treated at 200 mg QD.[50]

PF-06463922 was well tolerated. In the Phase 1 study, 11 (25%) of patients underwent dose delays, 8 (18%) had dose reductions, and 1 (2%) required dose discontinuation due to AEs. The most common treatment-related AE were hypercholesterolemia (14 patients, 47%), peripheral neuropathy (8 patients, 27%), and peripheral edema (7 patients, 23%). A total of 6 patients had treatment-related Grade 3 AEs, as 3 patients had Grade 3 hypercholesterolemia, and 1 patient each had Grade 3 lipase increased, hypophosphataemia, and dermatomyositis. There were no Grade 4 or 5 treatment-related AEs. There were 3 treatment-related serious adverse events: elevated lipase, seizure, and dermatomyositis.[50] Management of TEAEs related to PF-06463922 is outlined in Sections 5.6.1 and Section 5.4.4. Other TEAEs are noted in the PF-06463922 IB.[19]

As of the data cutoff date 20 April 2015, 44 patients (33 with ALK-positive NSCLC and 11 with ROS1-positive NSCLC) were enrolled across 7 QD dose levels and 3 BID dose levels, with total daily doses of 10–400 mg. 18 (41%) patients had one line of prior ALK or ROS1 TKI therapy and 19 (43%) having two or more prior lines of TKI therapy. 34 patients were evaluable for overall tumor response, and 25 for intracranial response; 27 patients were still receiving treatment as of the data cutoff date. In the 34 patients who were evaluable for response, the ORR was 44% (95% CI: 27–62), comprising 1 complete response, 10 confirmed partial responses, and 4 unconfirmed partial responses. An additional 6 patients (18%) had stable disease as their best response.

In 25 patients evaluable for intracranial responses, of whom 14 had CNS lesions as target lesions, the intracranial response rate was 36% (95% CI: 18–58), comprising 4 complete intracranial responses, 3 confirmed partial intracranial responses, and 2 unconfirmed partial intracranial responses (Pfizer, data on file[19]).

In one healthy volunteer in Study B7461008, the PR interval prolongation was associated with one episode of transient second-degree AV block (Mobitz type 1; Wenkebach). In one patient on clinical Study B7461001, the PR interval prolongation may have been associated

with the progression of pre-existing AV block to complete heart block. When the complete heart block was identified, the patient was immediately evaluated and subsequently treated by placement of an implanted pacemaker.

In response to the observation of PR interval prolongation, data from all available human studies (approximately 100 patients in clinical studies and 45 in single dose healthy volunteer studies) was reviewed. Additional instances were identified of asymptomatic increases in the PR interval, usually most notable during Cmax (1-2 hours post-dose). Of note, the patients with a PR interval > 200 msec were generally those with a baseline value at the upper end of the normal range.

The ECG changes appear limited to the PR interval, with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies, as described in the current IB.

Additional information may be found in the PF-06463922 IB[19] (2015) which is also to be considered the SRSD for PF-06463922.

1.2.3. Rationale for Studying Crizotinib in Combination with Avelumab in Patients with ALK-Negative NSCLC

Immune checkpoint inhibitors are demonstrating promising activity in a variety of tumor types, including NSCLC. It is becoming clear that combination strategies will be necessary for enhanced antitumor activity.[45,51] T cell suppression by immune checkpoint inhibitors may not be sufficient if not accompanied by T cell homing to tumor and their activation.[1,29,51]

Zhou et al recently identified ALK in a screen as one of the genes involved in suppressing T cell infiltrating the tumor.[46] T cells transduced with pooled shRNA libraries targeting negative regulators of T cell function were injected into B16 melanoma-bearing mice. Short hairpin RNA-driven CD8+ T cell accumulation in tumors more than doubled relative to peripheral lymphoid tissue when ALK was targeted. These results suggest that the same immunostimulatory effect may be achieved with pharmacologic inhibition of ALK.

Preliminary internal Pfizer data demonstrates synergistic activity of both crizotinib and PF-06463922 with PD-L1 blockade in a murine ALK-negative colon carcinoma syngeneic model, CT26 (Pfizer, data on file). Two independent studies have been conducted in CT26 murine model. In the first study, by Day 25 post-tumor inoculation, no statistically significant tumor growth inhibition (TGI) was observed when animals were treated with either crizotinib alone or murine anti-PD-L1 alone. The combination therapy resulted in 71.8% TGI (P value <0.0001). In the second study where the animals were treated with crizotinib dose escalation (5 mg/kg, 20 mg/kg, 40 mg/kg QD for 12 days) combining fixed murine anti-PD-L1 dose, by Day 25 post tumor inoculation no statistically significant TGI was observed from either murine anti-PD-L1 alone treatment or any dose of crizotinib alone treated groups comparing to isotype control antibody treated group. Murine anti-PD-L1 in combination with 5 mg/kg crizotinib treatment resulted in 59% TGI (P value <0.1), with 20 mg/kg crizotinib treatment resulted in 75.5% TGI (P value <0.001), and with 40 mg/kg crizotinib treatment resulted in 57.5% TGI (P value <0.1).

A third independent study has been done in MC38 colon carcinoma tumor model by using avelumab. Administration of murine avelumab alone resulted in 49.7% TGI, crizotinib alone resulted 48.5% TGI, and combination of murine avelumab with crizotinib led to 65% TGI.

The data described above suggests that crizotinib may enhance the activity of avelumab through an effect on T cell homing to tumor, independent of crizotinib's effect on tumor cells and independent of the presence of the mutation on the tumor parenchyma. In addition to ALK and/or Met, it is possible that other less well characterized targets of crizotinib may also contribute to the mechanisms through which crizotinib may enhance anti-tumor immunity. Therefore, the objective of Group A in the current study is to assess the safety and efficacy of the crizotinib-avelumab combination in a population lacking mutational targets on the tumor itself. In ALK-positive NSCLC, such an "immune-booster" activity of crizotinib would be difficult to distinguish from its direct effect on the ALK oncogenic driver in tumor cells. Therefore, in the current study, ALK-negative NSCLC patients will be enrolled in Group A, and care will be taken to ensure that patients with other known sensitivity mutations to crizotinib such as ROS1 or c-MET alterations are excluded or, if not known at the time of enrollment, identified retrospectively.

1.2.4. Rationale for Studying PF-06463922 in Combination with Avelumab in Patients with ALK-Positive NSCLC

Despite high response rates observed with crizotinib in the initial treatment of ALK-positive NSCLC-, progression of disease invariably occurs over time. This led to the development of-, new therapies. PF-06463922 is a next generation ALK inhibitor with enhanced activity against resistance mutations that arise upon treatment with first (crizotinib) and second generation (alectinib, ceritinib) ALK TKIs, as demonstrated in the Phase 1/2 trial presented at ASCO 2015.[50] (See Section 1.2.2.2).

Immune checkpoint inhibitors are demonstrating promising activity in a variety of tumor types, but the challenge remains in identifying optimal combinations with standard-of-care therapies including targeted agents. Tumor-directed therapies such as chemotherapy and targeted agents potentially improve tumor antigenicity by inducing cell death, providing the basis for potential synergy with immune checkpoint inhibitors.[45,47]

Additional preclinical data to support the combination of an ALK inhibitor and an immune checkpoint inhibitor comes from evaluation of ALK-driven mouse models of lung cancer. In this model, lung tumors containing ALK rearrangements induced an immunosuppressive microenvironment, regulating the expression of PD-L1 on the surface of lung tumor cells. This work suggested that combinations of ALK TKIs and immune checkpoint inhibitor therapies might represent an impactful approach for the treatment of ALK-driven NSCLC.[53]

Based on the promise of complimentary activity of ALK TKIs and immune checkpoint inhibitors[46,49] the MTD and RP2D of the combination of avelumab with PF-06463922 in ALK-positive NSCLC (Group B) will be assessed in the Phase 1b portion of this study. The safety of the combination will be further assessed in the Phase 2 portion as well as preliminary information on efficacy (ORR and CR rate). As the expected activity of

PF-06463922 is high in ALK-positive NSCLC in both pretreated and untreated patients, this study is not designed to assess the efficacy of the combination compared neither to PF-06463922 alone nor to avelumab single agent: the Phase 2 will be single arm, non-randomized and open label. For this reason, biomarker studies will be performed to determine whether there are biologic factors that may predict or confirm additive benefits of the combination versus single agents as well as all efficacy parameters, including Objective Response (OR) (CR, Partial Response (PR)), Disease Control Rate, Duration of response and landmark PFS and OS will be carefully assessed to correlate with any biomarker.

1.2.5. Rationale for Avelumab Starting Dose and Regimen

In this clinical trial, the avelumab starting dose will be 10 mg/kg administered as 1-hour intravenous (IV) infusions Q2W. This dose is the RP2D used on a total of 480 patients in the ongoing dose-expansion phase of study EMR 100070-001 (see Section 1.2.2.1 for details).

1.2.6. Rationale for Starting Crizotinib Dosing Regimen

Crizotinib starting dose will be 250 mg BID. This dose is the approved dose for treatment of ALK-positive metastatic NSCLC according to the crizotinib product label.

1.2.7. Rationale for Starting PF-06463922 Dosing Regimen

Based upon the current safety database and PK data, the starting dose for the combination will be 100 mg QD (See Section 1.2.2.3). In the ongoing PF-06463922 Phase 1 study, the 100 mg QD dose was well-tolerated and associated with antitumor activity.

1.3. Summary of Risk-Benefit Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

The risk-benefit relationship has been carefully considered in the planning of the trial. Based upon the avelumab preclinical and Phase 1 clinical data available to date, the conduct of the trial with the proposed avelumab dosing regimen is considered justifiable. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustifiable.

The clinical safety data available to date for single-agent avelumab in patients with advanced solid tumors suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of immune checkpoint inhibitors blocking the PD-1/PD-L1 axis (See Section 1.2.2.1 for more details). Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol.

Crizotinib is approved multinationally for the single-agent treatment of ALK-positive advanced NSCLC. Overall, the adverse event profile for crizotinib is considered generally tolerable and manageable. The most frequent adverse events include vision disorders,

nausea, diarrhea, constipation, vomiting, elevated transaminases, edema, fatigue, and decreased appetite.[18] Warnings and precautions noted using crizotinib include pneumonitis/ILD, transaminitis, QT interval prolongation and bradycardia.[18] Pneumonitis, diarrhea and liver toxicity represent possible overlapping toxicities with avelumab. Respective risk mitigation measures have been included in this protocol (Sections 5.5.1, Section 5.6.2 and Table 6).

PF-06463922 is being tested in an ongoing Phase 1 study in ALK-positive or ROS1-positive advanced NSCLC patients. Overall, the adverse event profile for PF-06463922 is manageable. The most frequent treatment-related adverse events were hypercholesterolemia, CNS EFFECTS, peripheral edema, peripheral neuropathy, hypertriglyceridemia, fatigue, nausea, ALT increase, and constipation. CNS EFFECTS is a cluster term comprising events including cognitive disorder, memory impairment, and slow speech.

Respective risk mitigation measures have been included in this protocol. Based on the current safety database, no overlapping toxicities with avelumab are anticipated. Respective risk mitigation measures have been included in this protocol (Sections 5.6.1, Section 5.6.3 and Table 7).

As noted above (Sections 1.2.3 and Section 1.2.4), preclinical rationale exists to support increased antitumor activity of avelumab in combination with crizotinib and with PF-06463922 in patients with ALK-negative NSCLC and ALK-positive NSCLC, respectively. Avelumab demonstrated an acceptable safety profile in the ongoing Phase 1 trial EMR100070-001. There is a potential for avelumab in combination with crizotinib and in combination with PF-06463922 to become an important therapeutic approach in patients with NSCLC. The projected benefit/risk of avelumab given in combination with crizotinib or PF-06463922 is favorable for investigation in this advanced cancer patient population.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

Phase 1b Primary Objectives**:**

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

Phase 2 Primary Objectives**:**

- Group A: To assess ORR per RECIST v.1.1 in previously treated locally advanced or metastatic ALK-negative NSCLC patients treated with the combination of avelumab and crizotinib at the RP2D;

- Group B: To assess ORR and CR rate per RECIST v.1.1 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/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]

- [redacted]
- [redacted]

2.2. Endpoints

Primary Endpoints

Phase 1b:

- First 2 cycles DLTs for Group A and Group B.

Phase 2:

- Confirmed OR per RECIST v.1.1 for Group A.
- Confirmed OR and CR per RECIST v.1.1 for Group B.

Secondary Endpoints

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 4); vital signs (blood pressure, pulse rate);

- Disease Control (DC), Duration of Response (DR), Time to Tumor Response (TTR), Progression-Free Survival (PFS) per RECIST v.1.1, and Overall Survival (OS);
- Pharmacokinetic parameters of crizotinib, its metabolite PF-06260182, and avelumab will be determined as data permit:
  - Maximum plasma concentration (C_{max}), time to maximum plasma concentration (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, as data permit;
  - C_{max}, T_{max}, AUC_{tau}, metabolite to parent ratio for AUC_{tau} ($MRAUC_{tau}$), and metabolite to parent ratio for C_{max} (MRC_{max}) for PF-06260182 following multiple doses in the presence of avelumab;
  - C_{max}, T_{max}, AUC_{tau}, AUC_{last}, CL/F, and V_z/F for PF-06463922 following multiple dosing in the presence of avelumab, if data permit; Single and multiple dose pharmacokinetics (C_{max}, C_{trough} of avelumab in the presence of crizotinib and PF-06463922).
- Avelumab anti-drug antibodies (ADA; neutralizing antibodies);
- Tumor tissue biomarkers, including but not limited to, PD-L1 expression and tumor infiltrating CD8+ T cells by immunohistochemistry (IHC).

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

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 as noted in Table 1 and Table 4. Determination of the MTD will be performed using the mTPI design as described in

Sections 3.1.1.1.1 and Section 3.1.1.2.1 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, pharmacodynamics and antitumor activity of the combination.

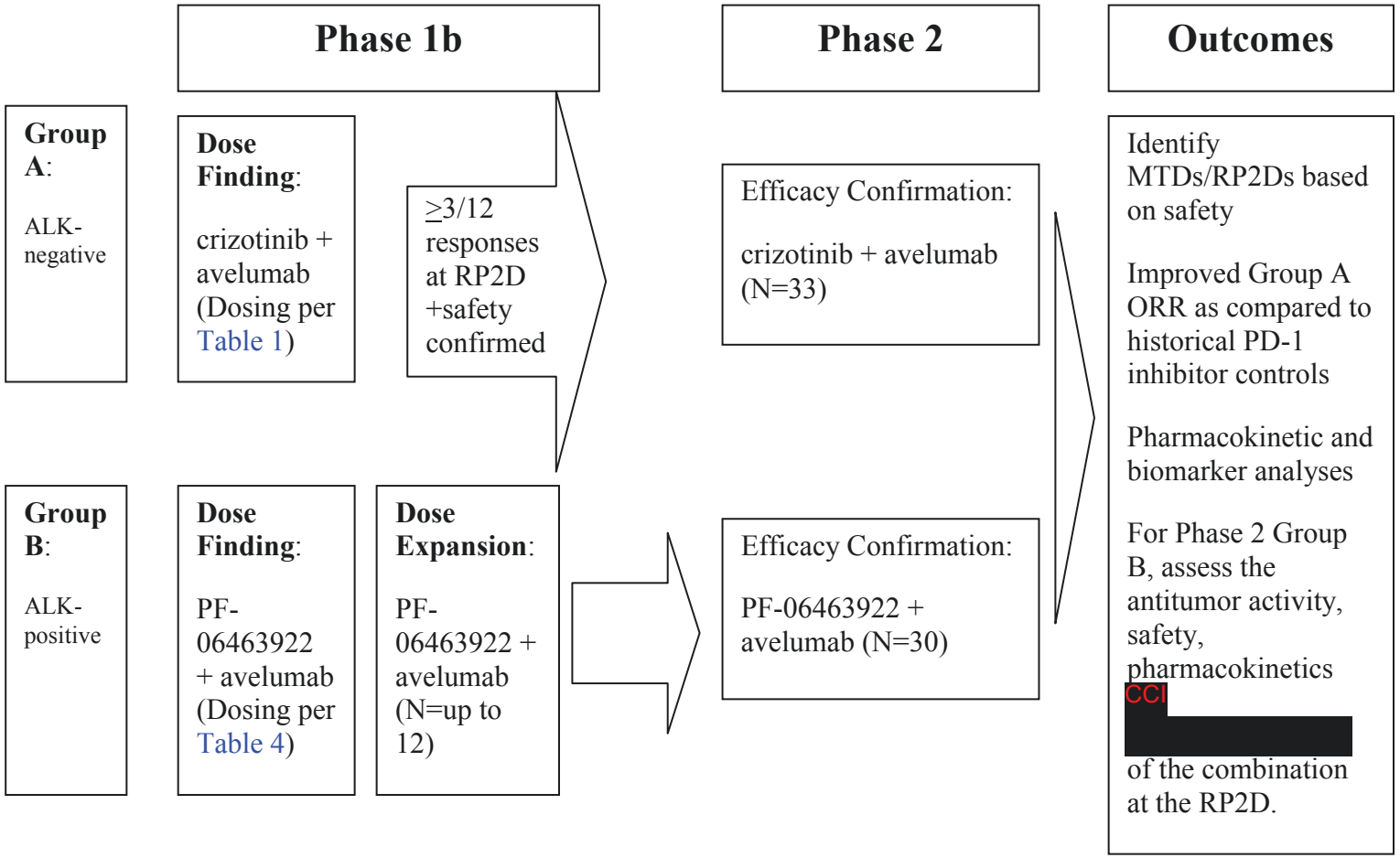
Phase 2 Group A :

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 or more patients of the 12 (≥ 25%) in Phase 1b have a confirmed objective response, then in Phase 2 an additional 33 patients will be enrolled and treated. If there are fewer than 3 patients (< 25%) who have a confirmed objective response in the first 12 patients treated at the RP2D, 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 the Phase 2 portion, to further assess the antitumor activity, safety, pharmacokinetics and pharmacodynamics of the combination at the RP2D.

Figure 1. Study Schema



3.1.1. Phase 1b Evaluation to Determine MTD/RP2D

3.1.1.1. Group A

The starting dosing regimens (DL-0) for the Group A combination are crizotinib 250 mg BID and avelumab 10 mg/kg IV Q2W in 2-week cycles.

3.1.1.1.1. Group A Dose Finding Criteria

Dose finding in Group A will follow an mTPI design, using dosing regimens of avelumab and crizotinib as shown in Table 1.

Table 1. Crizotinib plus Avelumab Dose Levels

	Avelumab	
Crizotinib	**5 mg/kg IV**	**10 mg/kg IV**
250 mg BID PO	DL-1A*	DL 0 (Start)
200 mg BID PO	DL-1A-1C	DL-1C**
250 mg QD PO	DL-1A-2C	DL-2C**

*-1A denotes dose reduction attributed to avelumab (A=avelumab)

**-1C denotes dose reduction attributed to crizotinib (C=crizotinib), -2C denotes dose reduction attributed to crizotinib (C=crizotinib).

Some of the possible dose finding scenarios based on the tolerability of the starting DL0 are illustrated in Table 2. In this dosing algorithm, there are up to 6 potential DLs. DL-1A and DL-1C will be explored only if the design recommends de-escalation already at DL0. DL-1A-1C and DL-2C will be explored only if the design recommends de-escalation at DL-1A and DL-1C. DL-1A-2C will be explored only if the design recommends to de-escalation at DL-1A-1C and DL-2C.

There are several potential dose-finding sequences for crizotinib and avelumab. The specific sequence to be followed depends upon the number of patients enrolled in the study and the number of DLTs observed at each specific DL combination. Some possible sequences are listed below in Table 2.

Table 2. Possible Dose Finding Sequences (Group A)

Possible sequences starting at Dose Level 0
DL0
DL0→ DL-1A and DL-1C
DL0→ DL-1A and DL-1C→ DL-1A-1C and/or DL-2C
DL0 → DL-1A and DL-1C→ DL-1A-1C and/or DL-2C→ DL-1A-2C

Dosing will begin at DL0 and may possibly be de-escalated to DL-1A and DL-1C according to Table 1. The patients who are enrolled in DL0 will be monitored for 2 cycles (4 weeks) for DLTs. If permitted by mTPI, this dose level will be expanded in cohorts of 3-6 patients to a total of 12 patients. Initially, 3 patients will be assigned to the DL (unless the first 2 patients experience a DLT) and monitored during the DLT period. If no more than 1 of the 3 patients has a DLT at the end of the DLT monitoring period, then, up to 3 more patients will be assigned to the same DL and followed for the DLT monitoring period. This will be followed by up to 6 more patients if there are no indications for DL change by the mTPI design. If at any point mTPI requires dose de-escalation, then initially up to 3 patients will be enrolled at lower dose levels (unless the first 2 patients experience a DLT) according to Table 1. In this case, both DL-1A and DL-1C may start concurrently. Dose re-escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

The re-escalation/de-escalation rules will follow the mTPI method (Section 9.2.1). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same DL to determine where future cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. The detailed dose-finding rules based on the mTPI are illustrated in Table 3.

Table 3. Detailed Dose Re-Escalation/De-Escalation Scheme

	Number of Patients Treated at Current Dose									
Number of DLTs	**3***	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
0	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	S	E
3	DU	DU	D	D	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S
6				DU	DU	DU	DU	DU	DU	D
7					DU	DU	DU	DU	DU	DU
8						DU	DU	DU	DU	DU
9							DU	DU	DU	DU
10								DU	DU	DU
11									DU	DU
12										DU

**If the first 2 patients both experience DLTs prior to enrollment of the third patient, then the dose should be de-escalated to the next lower dose level, as the current dose level will have exceeded the MTD*

E = Escalate to the next higher dose or if current dose level is DL0 stay on DL0.
S = Stay at the current dose.
D = De-escalate to the next lower dose level.
U = The current dose is unacceptably toxic.

Targeted DLT rate at MTD =30%.

As an example, if the total number of patients treated at DL0 is 3, then the following dosing rules are to be applied:

- 0 - 1 DLT → remain at the same DL (DL0);
- 2 DLTs → de-escalate to DL-1A and DL-1C and allow for possible re-escalation back to DL0;
- 3 DLTs → de-escalate to DL-1A and/or DL-1C as DL0 is intolerable.

Rules for dose finding using the mTPI method include the following:

- The target enrollment cohort size is 3-6 patients;
- The next cohort will be enrolled, if necessary, at the same dose level if allowed by mTPI design schema when each patient evaluable for DLT at the current dose cohort has been evaluated for the 2 cycles, or experiences a DLT, whichever comes first. The next cohort will receive the DL as assigned if a dose modification is required;
- If a patient does not receive at least 75% of the first 2 cycles doses of crizotinib or does not receive at least 2 infusions of avelumab within the DLT observation period (2 cycles = 28 days) for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level;
- Phase 1b is completed when 12 DLT-evaluable patients (see Section 9.1) have been treated at a DL confirmed to be safe.

3.1.1.1.2. Group A Phase 2

The Phase 1b of Group A will lead to the identification of the MTD or the RP2D. The first 12 patients treated at the MTD/RP2D will be assessed for objective response. If at least 3 patients (≥25%) achieve confirmed OR, then Phase 2 will be opened, and an additional 33 patients will be enrolled (45 in total). If there are <3 patients (<25%) with confirmed responses in Phase 1b, then Phase 2 will not open.

3.1.1.2. Group B

The starting dosing regimens (DL 0) for the Group B combination are PF-06463922 100 mg QD and avelumab 10 mg/kg IV Q2W in 2 week cycles.

3.1.1.2.1. Group B Dose Finding Criteria

Dose finding for Group B will follow an mTPI design, using a similar algorithm as described for Group A.

The starting DL0 for the Group B combination is PF-06463922 100 mg QD and avelumab 10 mg/kg IV Q2W in 2-week cycles (Table 4).

Table 4. PF-06463922 plus Avelumab Dose Levels (Group B)

	Avelumab	
PF-06463922	**5 mg/kg IV**	**10 mg/kg IV**
100 mg QD PO	DL-1A*	DL-0 (Start)
75 mg QD PO	DL-1A*-1P**	DL-1P**
50 mg QD PO	DL-1A*-2P**	DL-2P**

*-1A denotes dose reduction attributed to avelumab (A=avelumab)
**-1P, -2P denotes dose reduction attributed to PF-06463922 (P=PF-06463922)

Some of the possible dose finding scenarios based on the starting DL0 tolerability are illustrated in Table 5. In this dosing algorithm, there are up to 6 potential DLs. DL-1A and DL-1P will be explored only if the design recommends de-escalation at DL0. DL-1A-1P and DL-2P will be explored only if the design recommends de-escalation at DL-1A and DL-1P. DL-1A-2P will be explored only if the design recommends de-escalation at DL-1A-1P and DL-2P. There are several potential dose finding sequences for PF-06463922 and avelumab. The specific sequence to be followed depends upon the number of patients enrolled in the study and the number of DLTs observed at each specific dose combination. Some possible sequences are listed below in Table 5.

Table 5. Possible Dose Finding Sequences (Group B)

Possible sequences starting at Dose Level 0
DL0
DL0→ DL-1A and DL-1P
DL0→ DL-1A and DL-1P→ DL-1A-1P and/or DL-2P
DL0 → DL-1A and DL-1P→ DL-1A-1P and/or DL-2P→ DL-1A-2P

Dosing will begin at DL0 and may be possibly de-escalated to DL-1A and DL-1P according to Table 4. The patients who are enrolled in DL0 will be monitored for 2 cycles for DLTs. If permitted by mTPI, this dose level will be expanded in cohorts of 3-6 patients to a total of 12 patients. Initially, up to 3 patients will be assigned to the DL (unless the first 2 patients experience a DLT) and monitored during the DLT period. If no more than 1 of the 3 patients has a DLT by the end of the DLT monitoring period, then up to 3 more patients will be assigned to the same DL and followed for the DLT monitoring period. This will be followed by up to 6 more patients if there are no indications for a DL change by the mTPI design. If at any point mTPI requires dose de-escalation, then initially 3patients will be enrolled at lower dose levels (unless the first 2 patients experience a DLT). In this case, both DL-1A and DL-1C may start concurrently. Dose re-escalation will be allowed as long as the next highest dose level has not been determined to have exceeded the MTD.

The re-escalation/de-escalation rules will follow the mTPI method as described above in Section 3.1.1.1.1 and in Section 9.2.1. The detailed dose-finding rules based on the mTPI are illustrated in Table 3.

As an example, if the total number of patients treated at DL0 is 3, then the following dosing rules are to be applied:

- 0 - 1 DLT → remain at the same DL (DL0);
- 2 DLTs → de-escalate to DL-1A and DL-1P and allow for possible re-escalation back to DL0;
- 3 DLTs → de-escalate to DL-1A and DL-1P as DL0 is intolerable.

Rules for dose finding using the mTPI method include the following:

- The target enrollment cohort size is 3-6 patients;
- The next cohort will be enrolled, if necessary, at the same dose level if allowed by mTPI design schema when each patient evaluable for DLT at the current dose cohort have been evaluated for the 2 cycles, or experiences a DLT, whichever comes first. The next cohort will receive the DL as assigned if a dose modification is required;
- If a patient does not receive at least 75% of the first 2 cycles doses of PF-06463922 or does not receive at least 2 infusions of avelumab within the DLT observation period for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level;
- Phase 1b is completed when 12 DLT-evaluable patients (see Section 9.1) have been treated at a DL confirmed to be safe.

These patients will be followed for safety of the combination and to determine whether dose modifications of PF-06463922 and/or dose delays of avelumab are needed. This will allow for the determination of the RP2D.

3.1.1.2.2. Group B Expansion

The Phase 1b of Group B will lead to the identification of the MTD or the RP2D. Group B expansion cohort of approximately 12 additional patients will then be enrolled to further assess the safety, pharmacokinetics[redacted] and antitumor activity of the combination.

3.1.1.2.3. Group B Phase 2

Following the completion of Phase 1b, approximately 30 additional patients who are treatment-naive will be enrolled in the Phase 2 portion to further assess the antitumor activity, safety, pharmacokinetics [redacted] of the combination.

3.2. Dose-Limiting Toxicity Definitions

Severity of adverse events will be graded according to NCI CTCAE v4.03 (see Appendix 4). For the purpose of dose finding, any of the following adverse events 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.

3.3. Maximum Tolerated Dose Definition

The MTD estimate is the highest dose tested of crizotinib and avelumab or PF-06463922 and avelumab associated with the occurrence of DLTs within the first 2 cycles of treatment in <33% of patients.

3.4. Recommended Phase 2 Dose Definition

The RP2D is the dose of crizotinib and avelumab or PF-06463922 and avelumab in combination chosen for further clinical development. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, this dose may become the RP2D. Further experience in Phase 1b may result in a RP2D dose lower than the MTD.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis

   Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic:

   - Group A: ALK-negative NSCLC based on locally approved testing. No known ROS1 gene translocations, c-MET gene amplification,or c-MET exon 14 deletion

predicted to confer sensitivity to crizotinib (ROS1 and c-MET testing is not required if not locally available).

- EGFR mutations must also have been evaluated based on locally approved testing. Patients with EGFR mutation positive NSCLC will be permitted onto this study group if standard treatment options for EGFR mutation positive NSCLC have been exhausted.

- Group B: ALK-positive NSCLC based on locally approved testing.

2. Prior Therapy

   - Group A: At least 1 prior regimen of systemic therapy.

   - Group B Phase 1b: Any number of prior regimens, including zero.

   - Group B Phase 2: No prior systemic treatment for advanced or metastatic disease (adjuvant and/or neoadjuvant therapies are allowed if completed at least 6 months prior to study entry. No prior tyrosine kinase inhibitor therapy is allowed at any time prior to study entry)

3. Mandatory archival FFPE tumor tissue (all patients; see SoA and Section 6.1.1). If tissue is unavailable, a mandatory tumor biopsy must be performed.

4. At least one measurable lesion as defined by RECIST v.1.1 that has not previously been irradiated.

5. Age ≥18 years (≥20 years for Japan).

6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2 (see Appendix 2).

7. Estimated life expectancy of at least 3 months.

8. Adequate Bone Marrow Function, including:

   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;

   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;

   c. Hemoglobin ≥9 g/dL (may have been transfused).

9. Adequate Renal Function as evidenced by:

   a. Estimated creatinine clearance >30 mL/min as calculated using the Cockcroft-Gault equation.

10. Adequate Liver Function, including:

    a. Total serum bilirubin ≤1.5 x ULN;

    b. Aspartate and alanine aminotransferase (AST and ALT) ≤2.5 x ULN; in all patients.

11. Adequate Pancreatic Function, including:

    a. Serum amylase < 1.5 x ULN;

    b. Serum lipase < 1.5 x ULN.

12. Serum pregnancy test (for females of childbearing potential) negative at screening.

13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.

14. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Major surgery ≤4 weeks or radiation therapy ≤2 weeks prior to study entry. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 48 hours prior to patient registration.

2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways).

3. Systemic cytotoxic anti-cancer therapy ≤2 weeks, or any tyrosine kinase inhibitor ≤5 half-lives of the drug, before study entry. Any Group B patient who is taking PF-06463922 at the time of Screening may continue on that treatment until study entry (except for Group B Phase 2 where no prior tyrosine kinase inhibitor therapy is allowed).

4. Brain metastases, except:

    - Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable (Group A).

- Patients with asymptomatic brain metastases currently requiring steroid doses less than prednisone 10 mg daily or equivalent (Group B).

5. Persisting NCI CTCAE v4.03Grade >1 toxicity related to prior therapy; however, alopecia Grade 2 is acceptable.

6. Diagnosis of any other malignancy within 3 years prior to study entry, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration).

7. Current or prior use of immunosuppressive medication within 7 days prior to randomization, except the following: Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

8. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

9. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.

10. Rapidly progressive disease (eg, tumor lysis syndrome).

11. Gastrointestinal abnormalities including:

    - Inability to take oral medication;
    - Requirement for intravenous alimentation;
    - Prior surgical procedures affecting absorption including total gastric resection;
    - Treatment for active peptic ulcer disease in the past 6 months;
    - Active gastrointestinal bleeding, unrelated to cancer, as evidenced by clinically significant hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    - Malabsorption syndromes;
    - History of pancreatitis.

12. Known prior or suspected hypersensitivity to study drugs or any component in their formulations.

13. Active infection requiring systemic therapy.

14. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

15. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.

16. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

    Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥ 2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpms (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read ECG with QTc >470 msec, or congenital long QT syndrome.

17. History of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

18. Participation in other studies involving investigational drug(s) within 2 weeks prior to first administration of study combination therapy.

19. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea, colitis, inflammatory bowel disease, ulcer or pneumonitis) or psychiatric condition, including recent (withinthe past year) or active suicidal ideation or behavior, or end-stage renal disease or hemodialysis, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

20. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.

21. Pregnant female patients, breastfeeding female patients; male patients with partners currently pregnant; male patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of investigational product or longer based upon the compound’s half-life characteristics.

22. Current use of food or drugs that are known strong CYP3A4 inhibitors, including their administration within 10 days prior to the first dose of PF-06463922 or crizotinib (ie: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], ketoconazole, miconazole, itraconazole, voriconazle, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, bocepovir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

23. Current use or anticipated need for drugs that are known strong CYP3A4 inducers, including their administration within 12 days prior to the first dose (ie, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine and St. John's Wort).

24. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, such as astemizole*, terfenadine, cisapride*, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) within 12 days of administration of investigational products. [*withdrawn from US market]

25. Current use or anticipated need for drugs that are known P glycoprotein (P-gp) substrates with a narrow therapeutic index, including their administration within 12 days prior to study entry (eg, digoxin, dabigatran).

26. Prior organ transplantation including allogenic stem-cell transplantation.

4.3. Lifestyle Guidelines

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive crizotinib, which has been associated with teratogenic risk. Details are noted in the crizotinib IB.

Preliminary developmental toxicity studies using PF-06463922 have been completed in rats and rabbits. Embryonic and fetal toxicity (including embryo lethality, fewer and smaller viable fetuses with some external and visceral malformations) was observed in both species at all doses, where the low dose was projected to yield similar exposure as the recommended phase 2 dose of 100 mg once daily. Based on the study results, PF-06463922 induces embryonic and fetal toxicity in animals, and the current safety measures to prevent pregnancy should remain in place.

The teratogenic risk for avelumab is currently unknown. Two (2) methods of highly effective contraception must be used throughout the study and continue for at least 90 days after the last dose. The investigator or his or her designee, in consultation with the patient, will select two appropriate methods of contraception for the individual patient and his/her partner from the list of permitted contraception methods (see below) and instruct the patient in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her

designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly according to the Schedule of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential, defined as:

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure; or

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women. All other female patients (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 90 days after the last dose.

4.3.1. Sunlight Exposure

Patients treated with crizotinib and PF-06463922 should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period. Patients will be advised to report any reaction to sun-exposed skin.

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list in the Study Binder.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients will be provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is, therefore, intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For the purposes of this study, the investigational products are avelumab, crizotinib, and PF-06463922.

5.1. Allocation to Treatment

Allocation of patients to treatment groups will proceed based upon the presence or absence of ALK-positive NSCLC. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number, the patient number, and the date of birth of the patient. The site personnel will then be provided with a treatment assignment and/or dispensable unit (DU) or container number when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

5.2. Patient Compliance

A patient diary will be provided to the patients to aid in crizotinib or PF-06463922 dosing compliance. The diary will be maintained by the patient to include missed or changed doses.

Patients will be required to return all unused oral study treatments (crizotinib or PF-06463922). The returned oral study medication by the patient will be counted, documented, and recorded. The patient diary may also be used to support this part of the crizotinib or PF-06463922 accountability process.

The site will complete required dosage Preparation Record located in the Investigational Product (IP) Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer designated study monitor.

5.3. Investigational Product Supplies

Avelumab, crizotinib, and PF-06463922 will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and will be supplied by the sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines. Avelumab will be packed in boxes each containing one vial. The information on the trial drug will be in accordance with approved submission documents.

Avelumab will be shipped in transport cool containers (2°C to 8°C) with temperature monitoring devices.

5.3.1.2. Crizotinib

Crizotinib will be supplied for oral administration as capsules containing 200 mg or 250 mg of study medication and will be packaged in High-Density Polyethylene (HDPE) bottles.

5.3.1.3. PF-06463922

PF-06463922 will be supplied for oral administration as 25 mg tablets in High-Density Polyethylene (HDPE) bottles with desiccant.

5.3.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of investigational agents.

5.3.2.1. Avelumab

Avelumab will be administered in 14 day cycles at the investigational site.

The contents of the avelumab vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

For application in this trial, avelumab drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Investigational Product (IP) Manual.

Avelumab must not be used for any purpose other than the trial. The administration of trial drug to patients who have not been enrolled into the trial is not covered by the trial insurance.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

See the IP Manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.2.2. Crizotinib

Crizotinib will be dispensed at the beginning of every other 14-day treatment cycle (every 28 days). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Crizotinib will be provided in bottles containing 200 mg or 250 mg capsules. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Administration Cards and Patient Diaries. In addition, administration instructions will be detailed in the IP Manual.

5.3.2.3. PF-06463922

PF-06463922 will be dispensed at the beginning of every other 14-day treatment cycle (or every 28 days). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. PF-06463922 will be provided in bottles containing

25 mg tablets. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Administration Cards and Patient Diaries. In addition, administration instructions will be detailed in the IP Manual.

5.4. Administration

All trial treatments will be administered on an outpatient basis except for avelumab, and crizotinib or PF-06463922 on PK sampling visits, which will be administered at the Investigational site. The dose of study drug administered should never be higher than the original dose level assigned on Cycle 1 Day 1.

A cycle is defined as 14 days, regardless of missed doses or dose delays.

5.4.1. Avelumab

The IP Manual contains specific instructions for avelumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Avelumab will be administered on Day 1 of each cycle after all procedures/assessments have been completed as described in the Schedule of Activities table. Avelumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Avelumab will be administered as a 1-hour IV infusion once every 2 weeks. In order to mitigate infusion-related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate. Sites should make every effort to target infusion timing to be as close to 1 hour as possible. The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Sections 5.6.1.2 and Section 5.6.1.3.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle. If the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of study drug required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. Avelumab dose reduction for toxicity management is not permitted; however, next cycle administration may be omitted due to persisting toxicity as described in Table 6.

There is no change in the concentration of avelumab in the presence of food, thus it can be administered with or without food.

5.4.2. Crizotinib

Crizotinib will be administered orally BID or QD (See Table 1) at approximately the same time in the morning and evening 12 hours apart on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. On the study day in which both crizotinib and avelumab are administered, crizotinib should be taken in the morning prior to the avelumab infusion. A dosing card will be provided to the patients to provide guidance for the correct use of crizotinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

On PK sampling days, the crizotinib doses should be taken in the clinic under the supervision of the study site personnel.

Oral crizotinib will be administered with at least 8 oz (240 mL) of water with or without food.

5.4.3. PF-06463922

PF-06463922 will be administered orally QD (See Table 4) at approximately the same time of the day on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. On the study day in which both PF-06463922 and avelumab are administered, PF-06463922 should be taken in the morning prior to the avelumab infusion. A dosing card will be provided to the patients to provide guidance for the correct use of PF-06463922. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

On PK sampling days, the PF-06463922 dose should be taken in the clinic under the supervision of the study site personnel. The PF-06463922 dose should be administered after the 0 hour (pre-dose) pharmacokinetics (PK) sample has been collected. On electrocardiogram (ECG) assessment days, the PF-06463922 dose should be taken in the clinic under the supervision of the study site personnel so that timing of assessments is appropriately synchronized.

Since no clinically meaningful effect of food on the PK of PF-06463922 has been observed, PF-06463922 can be administered with or without food with approximately 8 oz (240 mL) of water.

5.4.4. Treatment after Initial Evidence of Radiologic Disease Progression

Immune checkpoint inhibitors agents such as avelumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm the observation. Assigned study treatment may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression.

Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging no longer shows PD, but rather CR, PR, or SD compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target as well as non-target lesions (refer to the Study Manual).

If the repeat imaging confirms PD, patients should be discontinued from study treatment. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with avelumab and crizotinib or avelumab and PF-06463922. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

5.4.5. Treatment after Confirmed Complete Response

Patients who have experienced a confirmed CR should continue to receive study treatment at the discretion of the Investigator. If the Investigator believes that a patient may benefit from avelumab treatment beyond 12 months, further treatment with avelumab may be permissible after discussion with the Sponsor. Patients in CR who have already stopped avelumab

treatment before completing the recommended 6 months of treatment after CR confirmation can resume treatment with avelumab at the same dose and schedule in order to complete the 6-month period. The recommended post-CR confirmation maximum treatment duration of 12 months applies to avelumab only. The treatment with crizotinib or PF-06463922 may continue without interruption at Investigator discretion.

5.5. Recommended Dose Modifications

Every effort should be made to administer investigational products on the planned dose and schedule. In the event that one of the combination agents is discontinued, the other agent may be continued at the discretion of the Investigator in consultation with the Sponsor.

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify their investigator at the first occurrence of any adverse event. If due to ongoing treatment-related toxicity and a dose delay is still necessary after 2 weeks, study treatment should be permanently discontinued, unless there is Investigator discussion of the clinical circumstance with the Sponsor and agreement that the patient may resume treatment after a lapse of greater than 2weeks. If a dose reduction is necessary, re-challenging at the original dose will only be permitted on a case-by-case basis after discussion and agreement between Investigator and Sponsor.

For avelumab, no dose modifications are permitted in this study, but doses may be delayed or omitted based on persisting toxicity. Crizotinib or PF-06463922 dose modifications as well as infusion omissions/delays for avelumab may occur independently from avelumab dose delays according to the guidance provided below and investigator's medical judgment and will be reported in the CRF. Dose levels for crizotinib and PF-06463922 dose modifications are provided in Sections 5.6.1, Section 5.6.2, and Section 5.6.3.

Some potential immune-related adverse events (irAEs) described with anti-PD-L1 drugs such as avelumab may overlap with crizotinib or PF-06463922 toxicities (eg, diarrhea, liver function tests increase, or pneumonitis). Any adverse event suspected to be immune-related should be managed according to the guidance for management of irAE as described below. For the crizotinib-avelumab combination in ALK-negative NSCLC, avelumab has proven clinical activity in this setting, therefore toxicity management guidelines are aimed to preserve avelumab dosing. Crizotinib dose interruptions may be necessary beyond what is recommended for single-agent crizotinib so that crizotinib-related toxicity does not lead to permanent discontinuation of avelumab. For the PF-06463922-avelumab combination in ALK-positive NSCLC, PF-06463922 has proven activity in this setting. Therefore, avelumab dose interruptions may be necessary to preserve PF-06463922 dosing. Specific guidance on treatment modifications for adverse drug reactions possibly associated to one or both of the study drugs including potential immune-related AEs are provided in Table 6 for avelumab with crizotinib combination and in Table 7 for avelumab with PF-06463922 combination.

5.5.1. Management of Avelumab + Crizotinib Treatment-Related Toxicity

See Section 5.6.2 for crizotinib dose modification and additional toxicity management guidance.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
Hematologic Abnormalities	Grade 1	Continue avelumab as per schedule.	Continue crizotinib at the same dose level
	Grade 2	Continue avelumab as per schedule.	Hold crizotinib until resolves to Grade ≤1, then resume at the same dose level.
	Grade 3	Withhold dose until toxicity is Grade ≤1 (or has returned to baseline), then resume treatment Exceptions are: Patients who develop Grade 3 or 4 lymphopenia without other dose limiting events (eg, opportunistic infection) may continue study treatment without interruption.	Withhold crizotinib dose until toxicity is Grade ≤1 (or has returned to baseline), then rechallenge at the same dose. **Exceptions are:** Patients who develop Grade 3 or 4 lymphopenia without other dose limiting events (eg, opportunistic infection) may continue study treatment without interruption.
	Grade 4	Permanent discontinuation Exceptions are: Single laboratory values out of normal range that are unlikely related to avelumab according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management.	Withhold crizotinib dose until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 dose level.
Avelumab infusion-related Reaction	Grade 1-4	See Section 5.6.1.2	Continue crizotinib at the same dose level
Avelumab hypersensitivity reactions	Grade 3-4	See Section 5.6.1.3	Continue crizotinib at the same dose level
Potential immune-related adverse events (irAEs)			
Liver Test Elevation (NCI-CTCAE v4)	**Grade 1** Grade 1 AST or ALT >ULN to 3.0 x ULN and/or total bilirubin >ULN	Continue avelumab therapy Continue liver function monitoring If worsens: Treat as Grades 2 or 3 to 4	Continue crizotinib at same dose level

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
	to 1.5 x ULN		
	Grade 2 AST or ALT >3.0 to ≤5 x ULN and / or total bilirubin >1.5 to ≤3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days If returns to Grade ≤1: Resume routine monitoring, resume avelumab therapy If elevations persist >5 to 7 days or worsen: Treat as Grade 3 to 4	Hold crizotinib, resume at the same dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks; (2) AST/ALT resolves to Grade ≤1; (3) bilirubin is <2x ULN.
	5.6. Grades 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.	Permanently discontinue crizotinib
Diarrhea/colitis	**Grade 1** Diarrhea: < 4 stools/day over Baseline	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Continue crizotinib at the same dose level. Symptomatic care with loperamide at the

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
	Colitis: asymptomatic	Close monitoring for worsening symptoms Educate patient to report worsening immediately If AE worsens: Treat as Grade 2, 3, or 4 below	Investigator's discretion
	Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment If improves to Grade ≤ 1: Resume avelumab therapy If persists >5 to 7 days or recurs: Treat as Grade 3 or 4.	Hold crizotinib, resume at the same dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) diarrhea has resolved to Grade ≤1
	Grade 3 or 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy If improves: Continue steroids until Grade ≤1, then taper over at least 1 month' resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). *Note: Infliximab should not be used in cases of perforation or sepsis*	Hold crizotinib, resume at a reduced dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) diarrhea has resolved to Grade ≤1
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal	Grade 1 or Grade 2	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement	Continue crizotinib current dose level

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
insufficiency, type I diabetes mellitus)		therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.	
	Grade 3 or Grade 4)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis) Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate. .	Hold crizotinib, resume at the same dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) AE has resolved to Grade ≤1
		• Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual	Hold crizotinib, resume at the same dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) AE has resolved to Grade ≤1

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections. Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.	
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) :	Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) Hormone replacement/suppressive therapy as appropriate Perform pituitary MRI and visual field examination as indicated Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone	Hold crizotinib, resume at the same dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) AE has resolved to Grade ≤1

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		replacement). Continue hormone replacement/ suppression therapy as appropriate.	
	If hypophysitis confirmed:	Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections. Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/ suppression therapy as appropriate.	
Rash	Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids) If persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper.	Continue at the same dose level Symptomatic therapy (eg, antihistamines, topical steroids) as needed

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		If worsens: Treat as Grades 3 to 4	
	Grades 3 Covering >30% body surface area;	Withhold avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections If improves to Grade 1: Taper steroids over at least 1 month; Resume avelumab therapy following steroids taper.	Hold crizotinib, resume at a reduced dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) rash has resolved to Grade ≤1 If recurs, permanently discontinue crizotinib
	Grade 4 Life threatening consequences	Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves to Grade ≤1: Taper steroids over at least 1 month	Hold crizotinib, then resume at a reduced dose level when rash has resolved to Grade ≤1 If recurs, permanently discontinue crizotinib.
Pneumonitis	Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4	Permanently discontinue crizotinib.
	Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 to 2.0 mg/kg/day prednisoneor equivalent. Add prophylactic antibiotics	Permanently discontinue crizotinib.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		for opportunistic infections Consider bronchoscopy, lung biopsy Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4	
	Grades 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).	Permanently discontinue crizotinib.
Renal irAEs	Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.	Continue Crizotinib at the same dose.
	Grade 2 to 3 Creatinine	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or	For Grade 2: Continue Crizotinib at the same dose.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
	increased > 1.5 and ≤ 6 x ULN	equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4	For Grade 3: Withhold Crizotinib dose until toxicity is Grade ≤ 1 (or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose
	Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	Withhold Crizotinib until toxicity is Grade ≤ 1 (or has returned to baseline), then reduce the dose by 1 level or discontinue at the discretion of the investigator.
Myocarditis	New onset of cardiac signs or symotoms and/or new laboratory cardiac biomarker elevation (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	Withhold Avelumab. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult. Consider myocardial biopsy if recommended per cardiology consult*. If symptoms improve, and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not imrprove/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.	Hold crizotinib until etiology is confirmed. If immune-mediated nature is excluded and symptoms improve to Grade ≤1, re-start crizotinib at the same or reduced dose based on clinical presentation and in consultation with the cardiologist. For isolated bradycardia or QTc prolongation, see dedicated guidelines further down in this table.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
	Immune-mediated myocarditis	Permanently discontinue avelumab Guideline based supportive treatment as appropriate as per cardiology consult*. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotocs for opportunistic infections. Once improving, taper steroids over at least 1 months. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).	If immune-mediated etiology is confirmed, hold crizotinib until steroids have been initiated and symptoms improve to Grade ≤1, then re-start crizotinib at the same or reduced dose based on clinical presentation and in consultation with the cardiologist.
*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001			
Other irAEs (not described above)	Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.	Continue at the same dose (Grade 2) or hold (Grade 3) Crizotinib pending clinical investigation. If irAE is ruled-out, re-start Crizotinib at the same dose (for Grade 3) If irAE is confirmed, treat as Grade 2 or 3 irAE
	Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.	Continue at the same dose (Grade 2) or hold (Grade 3) Crizotinib, depending on clinical diagnosis. Re-start Crizotinib at the same dose (for Grade 3) if symptoms improve to Grade ≤1
	Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	Hold Crizotinib until symptoms improve to Grade ≤1, then re-start Crizotinib at the same dose

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		Specialty consult as appropriate If improves to Grade ≤ 1: Taper steroids over at least 1 month.	
	Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult. If improves to Grade ≤ 1: Taper steroids over at least 1 month	Hold Crizotinib until symptoms improve to Grade ≤1, then re-start Crizotinib at the same dose
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	Hold Crizotinib until symptoms improve to Grade ≤1, then re-start Crizotinib at the same dose
Selected Adverse Drug Reactions Adverse events known to be associated with crizotinib described for crizotinib			
Visual disturbance	Grade 1/2	Continue avelumab on current schedule	Continue crizotinib at current dose level. Repeat ophthalmologic examination.
	Grade 3	Hold avelumab and resume when recovered to Grade ≤1	Interrupt crizotinib until recovery. Repeat ophthalmologic examination. Resume treatment by reducing by one dose level.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
	Grade 4	Permanently discontinue avelumab.	Discontinue crizotinib treatment and do not retreat. Repeat ophthalmologic examination.
Bradycardia (heart rate less than 60 beats per minute) in the absence of suspected or confirmed immune-mediated myocarditis. If immune-mediated myocarditis is suspected or confirmed, treat as described above	Grade 1	Continue avelumab on current schedule	Continue crizotinib at the same dose level
	Grade 2/3	Hold avelumab and resume when recovered to Grade ≤1	Withhold crizotinib until recovery to Grade ≤1 or to heart rate ≥60. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate ≥60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60.
	Grade 4	Hold avelumab and resume when recovered to Grade ≤1	Permanently discontinue crizotinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at the same dose level upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring. Permanently discontinue for recurrence.
Prolonged QTc , in the absence of suspected or confirmed immune-mediated myocarditis.	Grade 1	Continue avelumab on current schedule	Continue crizotinib at the same dose level
	Grade 2	Continue avelumab on current schedule	Continue crizotinib at the same dose level. Assess electrolytes and concomitant medications. Correct any

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
If immune-mediated myocarditis is suspected or confirmed, treat as described above			electrolyte or magnesium abnormalities.
	Grade 3	Hold avelumab and resume when recovered to Grade ≤1	Withhold until recovery to Grade ≤1, then resume at the same dose. In case of recurrence, withhold until recovery to Grade ≤1, then reduce 1dose level. Permanently discontinue in case of further Grade ≥3 recurrence.
	Grade 4	Hold avelumab and resume when recovered to Grade ≤1	Discontinue crizotinib treatment and do not retreat.
Other Non-Hematologic Toxicities and Laboratory Abnormalities			
	Grade 1	Continue as per schedule	Continue at the same dose level
	Grade 2	If a Grade 2 ADR resolves to Grade ≤1 by the last day of the current cycle, avelumab treatment may continue. If a Grade 2 ADR does not resolve to Grade ≤1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the patient should permanently discontinue treatment (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).	Hold crizotinib until resolves to Grade ≤1, then resume at the same dose level. If avelumab treatment is held and then restarted, crizotinib should only be restarted when the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) toxicity is resolved to Grade ≤1.
	Grade 3	Permanent discontinuation of avelumab **Exceptions are:** Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management. Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤1. Single laboratory values out of normal	Withhold crizotinib dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the Investigator.

Table 6. Management of Avelumab + Crizotinib Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	Crizotinib Treatment Modification
		range (excluding Grade ≥3 liver function test increase) 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.	
	Grade 4	Permanent discontinuation of avelumab, **Exceptions are:** single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.	Withhold crizotinib dose until toxicity is Grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the Investigator.

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB= creatine kinase muscle and brain b; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

5.6.1. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

See Section 5.6.3 for PF-06463922 dose modification and additional toxicity management guidance.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
Hematologic Abnormalities	Grade 1	Continue avelumab as per schedule.	Continue PF-06463922 at the same dose level
	Grade 2	Continue avelumab as per schedule	Continue PF-06463922 at the same dose level
	Grade 3	Withhold dose until toxicity is Grade ≤1 (or has returned to baseline), then resume treatment. For lymphopenia: If no evidence of infection or other clinically significant toxicity, continue at the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then resume treatment	Withhold PF-06463922 dose until toxicity is Grade ≤1 (or has returned to baseline), then rechallenge at the same dose For lymphopenia: If no evidence of infection or other clinically significant toxicity, continue at the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then rechallenge at the same dose.
	Grade 4	Permanent discontinuation Exceptions are: 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.	Withhold dose until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 dose level.
Avelumab infusion-related Reaction	Grade 1-4	See Section 5.6.1.2	Continue PF-06463922 at the same dose level
Avelumab hypersensitivity reactions	Grade 3-4	See Section 5.6.1.3	Continue PF-06463922 at the same dose level
Potential immune-related adverse events (irAEs)			
Liver Test Elevation (NCI-CTCAE v4)	Grade 1 AST or ALT >ULN to 3.0 x ULN and/or total bilirubin >ULN to 1.5 x ULN	Continue avelumab therapy Continue liver function monitoring If worsens: Treat as Grades 2 or 3 to 4	Continue PF-06463922 at same dose level
	Grade 2	Withhold avelumab therapy	Continue PF-06463922 at the

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
	AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Increase frequency of monitoring to every 3 days If returns to ≤Grade 1: Resume routine monitoring, resume avelumab therapy If elevations persist >5 to 7 days or worsen: Treat as Grade 3 or 4.	same dose level
	Grades 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.	Permanently discontinue PF-06463922 -.
Diarrhea/colitis	Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide) Close monitoring for worsening symptoms Educate patient to report worsening	Continue PF-06463922 at the same dose level.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		immediately If worsens: Treat as Grade 2, 3, or 4	
	Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment If improves to Grade ≤1: Resume avelumab therapy If persists >5 to 7 days or recurs: Treat as Grade 3 or 4.	Continue PF-06463922 at the same dose level.
	Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy. If improves: Continue steroids until Grade 1, then taper over at least 1 month. resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis	Hold PF-06463922 until symptoms improve to Grade 1, then resume PF -06463922 at the same dose level. If recurs, reduce or discontinue PF-06463922 treatment (at investigator discretion, upon consultation with the sponsor)
Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type	Grade 1 or Grade 2	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism),	Continue PF 06463922 at current dose level

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
I diabetes mellitus)		anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus), as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis) Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.	
	Grade 3 or Grade 4	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis) Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.	Continue PF 06463922 at current dose level
Hypopituitarism/ Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with	Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) Hormone replacement/ suppressive therapy as appropriate Perform pituitary MRI and visual	Continue PF 06463922 at current dose level

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
	inappropriately low ACTH)	field examination as indicated Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). Continue hormone replacement/suppression therapy as appropriate.	
	If hypophysitis confirmed	Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. Add prophylactic antibiotics for opportunistic infections Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.	Continue PF 06463922 at current dose level
Rash	Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids) If persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy	Continue PF-06463922 at the same dose level. Remind patient to avoid sunbathing, prolonged unprotected sun exposure, or tanning

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grades 3 to 4	
	Grade 3 Covering >30% body surface area	Withhold avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves to Grade ≤1: Taper steroids over at least 1 month; Resume avelumab therapy following steroids taper (for initial Grade 3).	Hold PF-06463922, resume at a reduced dose level when all of the following conditions are met: (1) avelumab has been resumed for at least 4 weeks, (2) rash has resolved to Grade ≤1 If recurs, permanently discontinue PF-06463922
	Grade 4 Life threatening consequences	Permanently discontinue avelumab therapy for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves to Grade ≤1: Taper steroids over at least 1 month;	Hold PF-06463922, then resume at a reduced dose level when rash has resolved to Grade ≤1 If recurs, permanently discontinue PF-06463922
Pneumonitis	Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious	Continue PF-06463922 at the same dose.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		Disease consults Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4	
	Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4	Withhold PF-06463922 until toxicity has returned to baseline. Then resume treatment at one dose level lower. Discontinue permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.
	Grades 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy If improves to Grade ≤1: Taper steroids over at least 1 month	Permanently discontinue PF-06463922.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).	
Renal irAEs	Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.	Continue PF-06463922 at the same dose.
	Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4	For Grade 2: Continue PF-06463922 at the same dose. For Grade 3: Withhold PF-06463922 dose until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose
	Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult If returns to Grade ≤1: Taper steroids over at least 1 month.	Withhold PF-06463922 until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 level or discontinue at the discretion of the investigator.
Myocarditis	New onset of cardiac signs or symotoms and/or new laboratory cardiac biomarker elevation (eg,	Withhold Avelumab. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and	Hold PF 06463922 treatment until etiology is confirmed.. If symptoms improve to Grade ≤1, and immune-mediated nature is ruled out, re-start PF-0463922 at the same or reduced dose based on clinical

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
	troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult. If symptoms improve, and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis	presentation and in consultation with the cardiologist.
	Immune-mediated myocarditis	Permanently discontinue avelumab Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).	If immune-mediated etiology is confirmed, hold PF 06463922 until steroids have been initiated and symptoms improve to Grade ≤1, then re-start PF 06463922 at the same or reduced dose based on clinical presentation and in consultation with the cardiologist.
*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001			
Other irAEs (not described above)	Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation If irAE is ruled out, manage as appropriate according to the	Continue at the same dose (Grade 2) or hold (Grade 3) PF-06463922 pending clinical investigation. If irAE is ruled-out, re-start

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.	PF-06463922 at the same dose (for Grade 3) If irAE is confirmed, treat as Grade 2 or 3 irAE
	Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.	Continue at the same dose (Grade 2) or hold (Grade 3) PF-06463922, depending on clinical diagnosis. Re-start PF-06463922 at the same dose (for Grade 3) if symptoms improve to Grade ≤1
	Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate If improves to Grade ≤ 1: Taper steroids over at least 1 month	Hold PF-06463922 until symptoms improve to Grade ≤1, then re-start PF-06463922 at the same dose
	Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult. If improves to Grade ≤ 1: Taper steroids over at least 1 month	Hold PF-06463922 until symptoms improve to Grade ≤1, then re-start PF-06463922 at the same dose
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal	Permanently discontinue avelumab therapy Specialty consult	Hold PF-06463922 until symptoms improve to Grade ≤1, then re-start PF-06463922 at the same dose

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
	replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer		
Selected Adverse Drug Reactions described for PF-06463922			
CNS effects	Grade 1/2	Continue avelumab	Continue PF-06463922 at the same dose or withhold dose until recovery to baseline.
	Grade 3	Interrupt avelumab until recovery to Grade ≤1.	Withhold PF-06463922 dose until toxicity is Grade ≤1. Reduce dose to the next lower dose level.
	Grade 4	Permanently discontinue avelumab.	Discontinue PF-06463922 treatment and do not retreat
Cholesterol increase (See Table 11 for statin recommendations)	Grade 1	Continue avelumab	Continue at the same PF-06463922 dose. Consider introducing use of a statin.
	Grade 2	Continue avelumab	Introduce the use of a statin and continue at the same dose.
	Grade 3	Continue avelumab	Introduce the use of a statin, or increase the dose of the statin, or change to a new statin. Either continue PF-06463922 at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.
	Grade 4	Continue avelumab	Increase the dose of the statin, or change to a new statin. Withhold dose until toxicity is Grade ≤2 and then reduce the PF-06463922 dose by 1 dose level or rechallenge at the same dose.
Triglyceride increase (See Table 11 for statin recommendations)	Grade 1	Continue avelumab	Continue at the same dose. Consider introducing use of a statin.
	Grade 2	Continue avelumab	Introduce the use of a statin and continue at the same dose.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
	Grade 3	Continue avelumab	Introduce the use of a statin, or increase the dose of the statin, or change to a new statin. Either continue PF-06463922 at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.
	Grade 4	Continue avelumab	Increase the dose of the statin, or change to a new statin. Withhold dose until toxicity is Grade ≤2 and then reduce the PF-06463922 dose by 1 dose level or rechallenge at the same dose.
Pancreatitis	Grade 1	Continue current dose of avelumab	Continue current PF-06463922 dose
	Grade 2	If elevated enzymes (both amylase and lipase are Grade ≥2) are observed in the absence of clinical symptoms or radiological findings of pancreatitis: continue avelumab. If elevated enzymes and radiologically confirmed pancreatitis, permanently discontinue avelumab and treat as Grade 3 or 4.	If elevated enzymes (both amylase and lipase are Grade ≥2) are observed in the absence of clinical symptoms or radiological findings of pancreatitis: continue at the same dose level. Repeat lipase and amylase and obtain pancreatic isoenzyme. If elevated enzymes and radiologically confirmed pancreatitis: withhold PF-06463922 dose. Repeat radiology and lipase and amylase and obtain pancreatic isoenzyme and if returned to baseline then resume treatment at one dose level lower.
	Grade 3 or 4	Permanently discontinue avelumab 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections If improves to Grade ≤ 1: Taper steroids over at least 1 month	Permanently discontinue PF-06463922
Other Non-hematologic	Grade 1	Continue as per schedule	Continue PF-06463922 at the same dose level.

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
Toxicities and Laboratory Abnormalities	Grade 2	If toxicity resolves to Grade ≤1 by the last day of the current cycle, treatment may continue. If toxicity does not resolve to Grade ≤1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the patient should permanently discontinue treatment (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).	Continue PF-06463922 at the same dose level
	Grade 3	Permanently discontinue avelumab, Exceptions are: Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which are controlled with medical management. Transient (≤24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolve to Grade ≤1. Single laboratory values out of normal range (excluding Grade ≥3 liver function test increase) 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. .	Withhold PF-06463922 dose until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 level or rechallenge at the same dose Patients who develop asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue PF-06463922 without dose modification at the discretion of the investigator. Nausea or vomiting must persist at Grade 3 or 4 despite maximal medical therapy to require PF-06463922 dose modification
	Grade 4	Permanently discontinue avelumab Exceptions are: single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days	Withhold PF-06463922 until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 level or discontinue at the discretion of the investigator. Patients who develop

Table 7. Management of Avelumab + PF-06463922 Treatment-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification	PF-06463922 Treatment Modification
		with adequate medical management.	asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue PF-06463922 without dose modification at the discretion of the investigator. Nausea or vomiting must persist at Grade 3 or 4 despite maximal medical therapy to require PF-06463922 dose modification

5.6.1.1. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion related reactions, a premedication regimen of 25 to 50 mg IV or oral equivalent diphenhydramine and 650 mg IV or oral equivalent acetaminophen/paracetamol (as per local practice) is mandatory approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

Following avelumab infusions, patients must be observed for 2 hours post infusion for potential infusion related reactions. Treatment recommendations for the management of infusion-related reactions and, severe hypersensitivity reactions, are outlined in Sections 5.6.1.2 and Section 5.6.1.3..

Investigators should also monitor patients closely for potential irAEs. Treatment recommendations for the management of irAEs are outlined in Section 5.6.1.4.

5.6.1.2. Management of Avelumab Infusion-Related Reactions

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 8.

Table 8. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Stop avelumab infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect bag infusion tubing from the patient. Avelumab treatment must be permanently discontinued.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for all subsequent infusions. .

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 8 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the Investigator may consider the addition of H2-blocker (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.6.1.3. Management of Avelumab-Related Severe Hypersensitivity Reactions

As with all monoclonal antibody therapies, avelumab can induce hypersensitivity reactions, including impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale/clammy skin, and cyanosis.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment, if required. Patient should be placed on monitor immediately and epinephrine injection and dexamethasone infusion should be available for immediate access.

5.6.1.4. Management of Avelumab Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v4.03).

Treatment of irAEs should follow guidelines set forth in Table 6 and Table 7.

5.6.2. Crizotinib Dose Modifications

Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as indicated in Table 9.

Table 9. Crizotinib Dose Levels for Intrapatient Dose Modifications

Crizotinib Dose Levels	Modified Dose Level
250 mg BID	200 mg BID
200 mg BID	250 mg QD
250 mg QD	Discontinue crizotinib

Patients requiring more than 2 dose reductions due to treatment-related toxicity will be discontinued from the study if these reductions occur during the DLT period. Otherwise, the patient may continue to receive avelumab as monotherapy at the Investigator's discretion and in consultation with the Sponsor.

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events (Table 6 and Table 7).

5.6.2.1. Nausea and Emesis

For nausea and emesis, treat with standard anti-emetics such as prochlorperazine or ondansetron. Taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered.

5.6.2.2. Diarrhea

For Grade 1 diarrhea, symptomatic care such as loperamide (Imodium) or no intervention at Investigator judgment should be considered. For Grade 2 diarrhea, loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours) should be administered. Refer to Table 6.

5.6.2.3. Bradycardia

For a heart rate <40 beats per minute, the patient should be evaluated fully including an assessment of concomitant medications. The dosage of any medication known to be associated with bradycardia, eg, beta-blockers, should be adjusted accordingly. If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold crizotinib dosing until recovery. Patient may continue treatment only with the agreement of both the sponsor and Investigator. Concurrent use of crizotinib with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible due to the increased risk of symptomatic bradycardia. Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia. See Table 6.

5.6.2.4. Pneumonitis/Pneumonia

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria;
- Blood culture should be performed in febrile patients;
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum);
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above);
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate;
- A plasma sample for BNP (B-type Natriuretic peptide) to evaluate for evidence of CHF;
- For Asian patients, a blood sample for β-D-glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis *jirovecii*);
- If clinically appropriate, high dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis.

For any case of drug-related pneumonitis, discontinue crizotinib and contact the Sponsor. See Table 6.

5.6.2.5. Renal Cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be performed at the time of the renal cysts diagnosis. Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

In addition, multitest dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter. In Korea, multitask dipstick urinalysis should be performed in all patients at screening and on Day 1 of each cycle thereafter. Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein if this is the local standard.

5.6.3. PF-06463922 Dose Modifications

Patients will be monitored closely for toxicity, and the dose of PF-06463922 may be adjusted as indicated in Table 10. Patients requiring dose reduction per Table 10 should undergo reduction to the next lower dose level as outlined below.

Table 10. PF-06463922 Dose Levels for Intrapatient Dose Modifications

PF-06463922 Dose Level	Modified Dose Level
100 mg QD	75 mg QD
75 mg QD	50 mg QD
50 mg QD	25 mg QD
25 mg QD	Discontinue PF-06463922

5.6.3.1. PR Interval Prolongation

If patients develop new first-degree AV block up to PR interval of 280 msec, then they should be monitored closely.

If patients develop new second-degree AV block or a PR interval >280 msec, then a timely and thorough assessment of concomitant medications and electrolytes should be made. If a dose reduction or treatment interruption is considered, then dose reduction may be preferred given the pharmacologic auto-induction observed with PF-06463922 and the potential for higher exposure of the first dose following a treatment interruption.

Additionally, for patients with PR interval prolongation, the concomitant use of medicinal products known to prolong PR interval is not advised and these should be used with caution (see Appendix 6).

5.6.3.2. Pancreatitis

Pancreatic acinar atrophy was identified in toxicology studies in both rodent and non-rodent species. Minimal to mild findings at clinically relevant concentrations are non-adverse (mid-dose in rats and all doses in dogs from 1-month study). The pathogenesis is considered distinct from acute pancreatitis, lacking inflammation or necrotic cell death.[19]

In light of these findings, careful monitoring of pancreatic enzymes amylase and lipase are recommended. If elevated enzymes (both amylase and lipase are Grade ≥2) are observed in the absence of radiological findings of pancreatitis, continue at the same dose level. Repeat lipase and amylase and obtain pancreatic isoenzyme.

If radiologically confirmed pancreatitis is noted, withhold dose of PF-06463922. Repeat radiology and lipase and amylase and obtain pancreatic isoenzyme and if returned to baseline then resume treatment at one dose level lower.

In the Phase 1 trial of PF-06463922 there was no radiographic findings of pancreatitis and no symptomatic pancreatic events.

5.6.3.3. CNS Effects

As potential of CNS effects and cognitive deficit were suggested in safety pharmacology and general toxicity studies, close clinical monitoring for signs and symptoms of neurological changes are recommended in the Phase 1 study. Most of the CNS effects, as demonstrated by changes in speech, memory, and mood, were mild to moderate in the Phase 1 study. Rarely, visual hallucinations have been reported. These were generally intermittent and limited, with management through withholding dose until these events resolved, followed by dose reduction. See Table 7.

5.6.3.4. Lipid Management

In the Phase 1 study, hypercholesterolemia was the most common adverse event. Elevations in lipids usually begin in the first few cycles and, if statins are not introduced, can rise to Grade 3 levels by the next treatment cycle. Therefore, the suggested management is to begin a statin for Grade 1 elevations in either cholesterol or triglycerides and to increase the statin dose if adequate control is not obtained, as outlined in Table 11 or introduce other lipid lowering agent as appropriate based on investigator's medical judgment as described in Table 7.

Members of the statin class of agents are differentially sensitive to CYP3A4 and the following table may be used to facilitate management of elevated lipids.

Table 11. Elevated Lipid Management

STATIN	CYP3A	Potential Effect* of PF-06463922 on statin AUC	Recommendation about Statin Selection and Dose**
Simvastatin (Zocor)	SENSITIVE Substrate	50-80% decrease in AUC	Selection not recommended
Lovastatin (Mevacor, Altocor)	SENSITIVE Substrate	50-80% decrease in AUC	Selection not recommended
Atorvastatin (Lipitor)	Substrate	40 % decrease in AUC	Consider increasing the atorvastatin dose (eg, 10 -->20 mg)
Pravastatin (Pravachol)	Substrate	30-40 % decrease in AUC	Consider increasing the pravastatin dose
Pitavavastatin (Livalo)	Not a Substrate	No change expected	No dose change
Rosuvastatin (Crestor)	Not a substrate	No change expected	No dose change
Fluvastatin (Lescol)	Substrate	~25 % decrease in AUC	No dose change

*Estimated based on the reported effect of strong and moderate CYP3A inducers on Statins.
** Dose adjustment to be based on changes in cholesterol levels (eg, worsening by 1 CTCAE grade level).

5.7. Investigational Product Storage and Accountability

The Investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secured area, under specified storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Storage conditions stated in the SRSD (ie, avelumab, crizotinib, or PF-06463922 IBs) will be superseded by newer label storage instructions.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be documented. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct patients on the proper storage requirements for take home study treatment.

5.7.1. Avelumab

Avelumab drug product must be stored in accordance with the avelumab investigational product label until use, with a temperature log maintained daily. Medication must be kept in a secured locked area at the study site in accordance with applicable regulatory requirements.

Avelumab must not be frozen. Rough shaking of avelumab must be avoided. Storage conditions stated in the SRSD (ie, IB will be superseded by the label storage).

5.7.2. Crizotinib

Crizotinib capsules must be stored in accordance with the crizotinib investigational label. Medication must be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Patients must be instructed to keep their medication in its original container and stored according to the label. Returned medication for crizotinib must be stored separately from medication that needs to be dispensed. Storage conditions stated in the SRSD (ie, IB will be superseded by the label storage).

To ensure adequate records, all study drugs will be accounted for in the CRF and drug accountability inventory forms as instructed by the Sponsor. The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Unless otherwise authorized by Pfizer, all crizotinib supplies unallocated or unused by the patients must be destroyed by procedures approved by Pfizer or returned to Pfizer or its designee. Patients must return all containers to a designated study center participant.

5.7.3. PF-06463922

PF-06463922 tablets must be stored in accordance with the PF-06463922 investigational product label. Medication must be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Patients must be instructed to keep their medication in its original container and stored according to the label. Returned medication must be stored separately from medication that is yet to be dispensed. Storage conditions stated in the SRSD (ie, IB will be superseded by the label storage).

To ensure adequate records, all study drugs will be accounted for in the CRF and drug accountability inventory forms as instructed by the sponsor. The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Unless otherwise authorized by Pfizer, all PF-06463922 supplies unallocated or unused by the patients must be destroyed by procedures approved by Pfizer or returned to Pfizer or its designee. Patients must return all containers to a designated study center participant.

5.8. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product/supplies.

5.9. Concomitant Treatment(s)

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for administration of the inactivated influenza vaccine.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

Concomitant treatment considered necessary for the patient's well-being may be given at the discretion of the treating physician.

Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Concurrent anticancer therapy with agents other than avelumab, crizotinib or PF-06463922 is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat infusion-related reactions, hypersensitivity reactions, flu-like symptoms, tumor lysis syndrome, and immune-related events are reported in Sections 5.6.1.2, Section 5.6.1.3, and Section 5.6.1.4.

5.9.1. Inhibitors and Inducers of CYP Enzymes

5.9.1.1. Group A

The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, telithromycin, troleandomycin, saquinavir, voriconazole, and grapefruit or grapefruit juice, are not allowed in the study. The topical use of medications, such as 2% ketoconazole cream, may be allowed when discussed with the Sponsor. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

Coadministration of crizotinib with CYP3A4 substrates with narrow therapeutic indices including, but not limited to, dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation.

Additionally, the concurrent use of non prescription drugs, complementary medicines (excluding vitamins) or herbal supplements is not recommended.

5.9.1.2. Group B

The *in vitro* studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of PF 06463922, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

Intial *in vitro* assessment for inhibition and induction drug-drug interaction potential indicated that PF 06463922 is a time-dependent inhibitor of CYP 3A and also an inducer of CYP3A and CYP2B6. The net effect of PF-06463922 on CYP3A is currently under investigation. At substantially higher concentrations than those observed clinically, PF-06463922 also inhibited CYP2C9 in *in vitro* studies.

To protect patient safety, the following action should be exercised until more information is available:

- Coadministration of strong CYP3A inhibitors (eg, atazanavir, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, miconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos]) is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely needed during the study, strong CYP3A inhibitors should be used with caution and patient closely monitored for safety. Caution should be excercised exercised when coadministering drugs that are moderate CYP3A inhibitors (eg: amprenavir, aprepitant, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, fosamprenavir imatinib, verapamil). Closely monitor the safety of patients and reduce the PF-06463922 dose if necessary.

- Coadministration of strong CYP3A4 inducers (eg, strong inducers: carbamazepine, phenobarbital, phenytoin, rifatutin, rifampin, St. John's Wort) is not permitted at study entry. The use of these and other strong CYP3A4 inducer drugs concomitantly with PF-06463922 during the study is strictly prohibited and alternate medications should be considered. If absolutely necessary, administration of PF-06463922 must be stopped while receiving the strong inducer and PF-06463922 must not be restarted until 10 days after the end of treatment of the strong CYP3A inducer. Caution should be exercised when coadministrating drugs that are moderate CYP3A inducers (eg: nafcillin, modafinil, etravirine, efavirenz, bosentab, etc). Closely monitor the safety of patients and adjust the PF-06463922 dose if necessary.

- Caution should be exercised when co-administer co-administering drugs that are sensitive CYP2B6 substrates such as bupropion and efavirenz. The safety of patients should be closely monitored and the dose could be adjusted if necessary.

- PF-06463922 inhibits CYP2C9 (in vitro); caution should be excercised when co-administering drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or celecoxib. The safety of patients should be closely monitored and the dose could be adjusted if necessary.

- Coadministration of PF-06463922 with CYP3A substrates with a narrow therapeutic index, such as alfentanil, astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* (*withdrawn from US market) is not permitted starting from the first PF-06463922 dose and until 12 days after the last PF-06463922 dose. Alternate medications should be considered. Temporary use (<7 days) of drugs with adjustable dosing regimens, such as fentanyl, is allowed during PF-06463922 treatment, but the dose should be carefully adjusted to reach therapeutic effect and manage potential side effects of the narrow therapeutic index drug. If there is any interruption or change in PF-06463922 treatment, the dose of the CYP3A substrate with narrow therapeutic index and adjustable dosing regimen may need to be adjusted down in dose .

- The results from *in vitro* studies showed that PF-06463922 is a P-gp inhibitor. The concurrent use of drugs which are P-gp substrates with narrow therapeutic indices, such as digoxin and dabigatran is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely needed during the study, caution should be exercised when co-administered P-gp substrates with narrow therapeutic indices with PF-06463922. PF-06463922 may increase the plasma concentrations of these drugs and patients should be closely monitored for safety and dose of the P-gp substrate with a narrow therapeutic index may need to be stopped or adjusted if necessary.

- Coadministration of known strong CYP2C19 inhibitors, such as fluconazole, fluvoxamine, and ticlopidine should be avoided and alternate drugs should be considered. If their use becomes necessary, this should be done with caution since they may increase PF-06463922 plasma concentrations.

- Coadministration of known strong CYP2C8 inhibitors, such as gemfibrozil, should be avoided. If their use becomes necessary, this should be done with caution since they may increase PF-06463922 plasma concentrations.

Any questions regarding the use of alternative medications should be directed to the Sponsor for guidance.

5.9.2. Other Anti-Tumor/Anti-Cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

5.9.2.1. Other Prohibited Concomitant Medications and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy;
- Radiation therapy (with the exception noted in the Concomitant Radiotherapy Section 5.9.5);
- Immunotherapy, immunosuppressive drugs [unless otherwise indicated for the treatment of irAEs (Section 5.9.6.)], or other experimental pharmaceutical products (ie, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs);
- Any vaccine therapies for the prevention of infectious disease except for inactive vaccines ;
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin);
- Acetaminophen use should be restricted to no more than 2 g/day;
- Testosterone replacement therapy is only allowed in Group A in the presence of signs and symptoms clearly attributable to hypogonadism in consultation with an endocrinologist, who should also exclude any potential confounding effects of elevated prolactin and/or estradiol, or a significant recent change in corticosteroid dose, before doing so;
- The concurrent use of crizotinib (Group A) with medicinal products that are known to prolong the QT interval, and/or antiarrhythmics should be used with caution. The use of crizotinib in combination with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible, due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension).

5.9.3. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 4 weeks (2 cycles) of treatment but they may be used at any time to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[39]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the investigator in line with local guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator.

5.9.4. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study.

In case of surgical procedure avelumab treatment should be delayed. Reinitiation should be discussed with the Sponsor.

The appropriate interval of time between surgery, crizotinib, and PF-06463922 required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping crizotinib or PF-06463922 is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate crizotinib or PF-06463922 treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery, but resumed no sooner than 48 hours after surgery.

5.9.5. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

- Crizotinib must be stopped 24 hours before and at least 24 hours after complete of radiation therapy.

- PF-06463922 treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

5.9.6. Clarification About Steroid Use

Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes.[22,34] Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes. Therefore, if a study patient is still receiving avelumab the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs is permitted according to the modalities indicated in Table 7;

- Physiologic use: replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable;

- Prophylactic use, eg, for the prevention of acute infusion-related reactions is prohibited.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities and ASSESSMENTS section.

6.1.1. Tumor Biospecimens

Provision of an archival FFPE tumor tissue sample is required from all patients prior to registration. The archival tumor tissue specimen may be from either a primary or metastatic lesion, and may represent tissue obtained at the time of, or subsequent to, the initial diagnosis. The archival tumor tissue collection should be within one year of start of study treatment, with no intervening systemic anti-cancer therapy (including neoadjuvant or adjuvant therapy). If an older archival tumor tissue (>1 year prior to start of study treatment) is available, it might still be submitted but will not fulfill requirement for tumor tissue. Archived tumor tissue should be provided as a FFPE tumor tissue block containing sufficient tumor tissue to allow if possible for sectioning of fifteen (15) slides each containing a 5-micron tissue section. If a tissue block cannot be provided, sites should try to obtain 15 unstained slides each containing a 5-micron tissue section cut serially from the same block. If archived FFPE tissue is not available, a *de novo* (ie, fresh) tumor sample must be obtained in accord with local institutional practice for tumor biopsies. Archival or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted

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6.1.2. Determination of NSCLC Molecular Status

ALK status will be determined by local standards. Retrospective central laboratory testing for alterations in ROS1, c-Met genes (including ROS1 gene translocation, c-Met gene amplification, and c-Met exon 14 deletion), and EGFR will be performed on all tumor tissues for validation of mutational status.

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

6.3. End of Treatment/Withdrawal and Follow-Up Visits

For End of Treatment/Withdrawal procedures, see Schedule of Activities (SOA) and ASSESSMENTS section.

6.4. Patient Withdrawal

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol- required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment per the Investigator will be eligible to continue with avelumab in combination with crizotinib or avelumab in combination with PF-06463922, provided that the treating physician has determined that the benefit/risk for doing so is favorable and discussed with the Sponsor (See Table 7);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the Sponsor) may continue treatment with the other study treatment;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient refuses further visits, the patient should continue to be followed for survival (if survival is a secondary endpoint) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study specific evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5. Follow-up Visits

For follow-up procedures see Schedule of Activities and ASSESSMENTS section.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team and Sponsor will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, 12-lead ECG, laboratory assessments, including pregnancy tests and verification of concomitant treatments.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting study treatment, once at the start of screening and once at the baseline visit immediately before investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at every treatment cycle prior to dosing, during the active treatment period, at the end of study treatment, during follow-up (up to 90 days after last study treatment) and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from treatment but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.2.1. Avelumab Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 5.6.1.4. AESIs are reported according to the general AE reporting rules specified in Section 8.14.1.

7.1.3. Laboratory Safety Assessment

Haematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities (SOA) and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 12.

Table 12. Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	Protein, glucose and blood Urine dipstick for urine blood: If positive, collect microscopic urinalysis (Reflex Testing)	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Calcium*			
	Total Bilirubin*			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Phosphorus or Phosphate*			
	Albumin*			
	Total Protein*			
	Uric Acid*			
	Amylase*			
	Gamma glutamyl transferase (GGT)*			
	Cholesterol*			
	Creatine kinase*			
	Lactate dehydrogenase (LDH)*			
	Lipase*			
	Triglycerides*			
	HBV, HCV			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH			

°Potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, and acetaminophen levels.
^ Serum total amylase (pancreatic isoenzyme required if serum total amylase >1.5x ULN per local institutional ranges (ie, CTCAE Grade >1)).
ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, -free thyroxine (FT4), GGT=gamma-glutamyltransferase, HBV= hepatitis B virus, HCV= hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, RF=rheumatoid factor, TSH=thyroid-stimulating hormone, WBC=white blood cell.

7.1.4. Vital Signs and Physical Examinations

Patients will have a physical examination to include major body systems, weight, blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the Schedule of Activities. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

7.1.5. 12-Lead Electrocardiograms

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. All patients require a single ECG measurement at screening. Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all other ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to ≤500 msec. Patients will then restart the investigational product at the next lowest dose level or dose delayed as appropriate for specific investigational product. If the QTc interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. Additional ECGs will be performed as clinically indicated. Clinically significant findings seen on the follow up ECGs should be recorded as adverse events. Prior to concluding that an episode of prolongation of the QTc interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist.

If a patient experiences PR prolongation >200 msec or second-degree or third-degree AV block, refer to Section 0.

If a patient experiences any cardiac or neurologic AEs (especially syncope, dizziness, seizures, or stroke), an ECG in triplicate should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.2. Pharmacokinetics Assessments

Plasma/serum samples will be obtained from patients for PK depending on the treatment group.

7.2.1. Blood Sample Collection for Pharmacokinetic Analysis

Where noted in the Schedule of Activities, blood samples will be collected at approximately the same time as other assessments wherever possible.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or serious AE's and the date and time of blood sample collection and of last dosing prior to PK collection documented in the CRF.

Where noted in the Schedule of Activities, blood samples for study drug concentrations will be collected at approximately the same time as other assessments such as pharmacodynamic samples, ECGs and bone marrow aspirate collections etc., wherever possible.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

If patient discontinues either PF-06463922/crizotinib or avelumab therapy, PK samples for the discontinued drug is no longer necessary.

PK samples will be assayed using a validated analytical method in compliance with Pfizer standard operating procedures. Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the Lab Manual.

7.2.2. Collection of Avelumab Pharmacokinetic Samples (Both Groups A and B)

Blood samples (3.5 mL whole blood) will be collected for PK analysis of avelumab into an appropriately labeled serum separator tube (SST) as outlined in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, with the exception of samples where nominal time coincides with end of infusion, samples obtained within ±10% of the nominal time (eg, within 3 minutes of a 30 minute sample) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). For samples where nominal time coincides with end of infusion, a sample collected within 10 min post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If the infusion of avelumab is interrupted due to AE, any PK samples scheduled during the time the AE is occurring are not required. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

- CCI [redacted]

7.2.3. Collection of Crizotinib Pharmacokinetic Samples (Only Group A)

Whole blood (3 mL) will be collected into an appropriately labeled K_2EDTA tube at the designated times as outlines in the Schedule of Activities to provide at least 1 mL of plasma for crizotinib PK analysis. These samples will be analyzed for crizotinib and its metabolite PF-06260182.

Special precaution should be taken to minimize crizotinib samples from exposure to visible light, which will cause rapid degradation of crizotinib.

7.2.4. Collection of PF-06463922 Pharmacokinetic Samples (Only Group B)

Whole blood (4 mL) will be collected at the designated times as outlined in the Schedule of Activities to provide at least 2 mL of plasma for PF-06463922 PK analysis.

Special precaution should be taken to minimize PF-06463922 sample from exposure to visible light, which will cause rapid degradation of PF-06463922.

7.3. Immunogenicity Assessment

Blood samples (3.5 mL whole blood) will be collected for assessment of avelumab Anti-Drug Antibodies (ADAs) into an appropriately labeled serum separator tube (SST). Predose ADA samples will be collected within 2 hours prior to dosing. At each assessment, a single ADA sample will be separated into two aliquots in order to assess both ADA and nAb (if warranted, see below). Further details can be found in the Lab Manual. This assessment will take place at regular intervals during the treatment and follow-up periods as described in the Schedule of Activities.

A tiered ADA testing strategy will be used: all samples that are positive in the screening assay will be confirmed for antibody specificity. Confirmed positive samples will be further characterized for titer and tested in the neutralizing antibody (nAb) assay, if appropriate.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

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7.4. Translational and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of avelumab and either crizotinib or PF-06463922. CCI [redacted]

7.4.1. Tumor Tissue

Tumor biospecimens from archived tissue samples and/or *de novo* biopsies (see Section 6.1.1) will be used to analyze candidate CCI [redacted] protein markers, or relevant signature of markers, for their ability to identify those patients who are most likely to benefit from the study treatment. CCI [redacted] Markers that may be analyzed include, but may not necessarily be limited to, PD-L1 expression and CD8+ TILs.

Acquisition of the mandatory tumor tissue may be completed prior to the 28 day screening window, but it is required for patient enrollment. Note that if archival FFPE tumor tissue cannot be provided, FFPE tumor tissue from a de novo tumor biopsy performed at screening must be provided.

Only core needle or excisional biopsies, collection of malignant pleural effusion cell pellets, or resection specimen are suitable (Endobronchial Ultrasound Guided Transbronchial Core Needle biopsies are adequate). Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Laboratory Manual.

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7.6. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans. Baseline CNS imaging is required to identify asymptomatic brain metastases. CT or MRI scans are to be done starting at Cycle 4/Week 8 (+1 week) then repeated every 4 cycles/8 weeks (±1 week). Bone scans will be performed (or bone MRI if preferred by Investigator) at baseline and on study if bony metastases are suspected. Patients with positive results on the bone scans (or bone MRI if preferred by Investigator) will have these repeated every 8 cycles/16 weeks (±1 week).

Tumor assessments must continue until disease progression has been determined by the radiologist regardless of initiation of subsequent anti-cancer therapy. For patients who stop study treatment without PD, tumor assessments will be evaluated for delayed tumor response by avelumab. Tumor assessments must continue if the treating physician determines the patient would benefit clinically from treatment beyond RECIST (See Appendix 3) v.1.1-defined disease progression (see Section 5.4.4). Both target and non-target lesions are to be followed using the same modality used at baseline and interval unless clinically indicated. Tumor assessments should be repeated after at least 4 weeks to confirm response and disease progression, and at the End of Treatment visit if more than 4 weeks have passed since the last evaluation. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD.

All radiographic images will be collected and may be objectively verified by a blinded independent third-party core imaging laboratory as described in the Imaging Manual.

CCI [redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. -SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasations;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

The guidance on reporting of medication errors also applies to the reporting of overdose.

For purposes of this study, an overdose of avelumab is defined as an increase ≥5% than the planned avelumab dose for that particular administration.

As for crizotinib and PF-06463922, an overdose is defined as a dose greater than the prescribed dose.

There is no specific treatment for avelumab, crizotinib, or PF-06463922 overdose. In the event of overdose with any of these study drugs, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided as clinically indicated.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing outside of protocol-stipulated dose adjustments or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect;

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE) Grade 5 (see the section on Severity Assessment).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For patients with preexisting AST or ALT baseline values above the normal range, AST or ALT value ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller);

Concurrent with

    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, headache may be severe (interferes significantly with the patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational

product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for the termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Sections 6.3 and Section 6.4)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis Sets

The following patient populations will be assessed:

- Full analysis set: includes all enrolled patients who receive at least 1 dose of study treatment. If a patient received more than one study treatment the patient will be classified according to the first study treatment received. This will be the primary analysis set for all efficacy endpoints in both Phase 1b and 2;

- Safety analysis set: includes all enrolled patients who receive at least 1 dose of study treatment. If a patient received more than one study treatment the patient will be classified according to the first study treatment received. In this non-randomized study the Full analysis set and the Safety analysis set are identical. This will be the primary analysis set for all safety endpoints in both Phase 1b and 2;

- DLT-evaluable analysis set includes all patients enrolled in Phase 1b who are in the safety analysis set, and either experience DLT during the first 2 cycles, or complete the observation period for the first 2 cycles of treatment. If there is a patient without DLTs and who does not receive at least 75% of the first 2 cycles doses of crizotinib or PF-06463922 or who do not receive at least 2 infusions of avelumab for reasons other than study drug-related toxicity will be replaced;

- PK analysis set: includes all patients in the safety analysis set who have sufficient concentration data to estimate at least 1 of the PK parameters of interest;

- Biomarker analysis set: includes all patients in the safety analysis set who have at least 1 screening biomarker assessment, and have received at least 1 dose of any study drug. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose De-Escalation/Re-Escalation: mTPI

Many alternative designs have been proposed to the standard 3+3 design for Phase 1 dose escalation studies that improve its accuracy, efficiency and statistical validity.

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 (p_T) rate (p_T = 0.30). If the toxicity rate of the currently used dose level is far smaller than p_T, the mTPI will recommend escalating the dose level; if it is close to p_T, the mTPI will recommend continuing at the current dose; if it is far greater than p_T, 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. As shown by Ji and Wang, mTPI design is more efficient and safer than 3+3 design.[53] They considered 42 scenarios to cover a wide range of practical dose-response shapes, and concluded that the 3 + 3 design was more likely to treat patients at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3 + 3 design exhibited a lower overall toxicity percentage than the mTPI design in only one of 42 scenarios.

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.[20] Thus, compared to

other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement. Recently, a Phase 1 study based on the mTPI design has been published.[20]

Decision rules 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 $(0, p_T-e_1)$, the overdosing interval $(p_T+e_2,1)$, and the proper-dosing interval $(p_T- e_1, p_T+ e_2)$, where e_1 and e_2 are small fractions. Based on the safety profile of crizotinib and avelumab, e_1 is selected as 0.05, and e_2 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), overdosing corresponds to a dose de-escalation (D), and proper dosing 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.[20] 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).

The Phase 1b dose finding evaluation of the trial 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 to toxic, as determined by the DLT rate and/or lower than expected doses of the study treatments. In case de-escalation is required from the initial starting DL0, it is estimated that up to approximately 42 DLT-evaluable patients will need to be enrolled to estimate MTD for the crizotinib plus avelumab combination. For the PF-06463922 plus avelumab combination, up to approximately 36 patients may be enrolled.

9.3. Sample Size Determination

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

For Group A, it is expected that from 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 (See Sections 3.3 and Section 3.4) according to the safety of the combination. These patients will also be monitored to assess objective response in order to determine the expansion into Phase 2, an additional 33 patients enrolled at the RP2D in Stage 2 (Phase 2). The sample size determination is based on Simon's Optimal Two-Stage design.[38] The null hypothesis that the true ORR does not exceed 15% will be tested at α=0.025 (one-sided) against the alternative:

H0: ORR≤15% versus Ha: ORR>15%

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 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 will be rejected if there are 12 patients with confirmed CR or PR among 45 patients treated at the RP2D. The study will have at least 80% power to reject the null hypothesis when the true response rate ORR is at least 35% (Ha: ORR≥35%).

For Group B, it is expected that from approximately 12 to 36 patients will need to be treated in the dose-finding stage of Phase 1b using the mTPI approach. Up to 12 additional patients may be enrolled at the MTD to further characterize safety and tolerability and determine the RP2D (See Section 3.3 and Section 3.4).

For the Phase 2 of Group B, approximately 30 treatment-naïve patients will be enrolled. This will allow estimating the ORR and CR rate with a maximum standard error of 9.1%. Table 13 provides the exact binomial 90% and 95% confidence intervals for the ORR and CR rate based on different bserved responses among 30 patients.

Table 13. 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%)

9.4. Efficacy Analysis

The Full analysis set will be used for all efficacy analyses. Summaries of efficacy will be presented separately for Group A (including Phase 1b and Phase 2 patients at the RP2D) and Group B (including Phase 1b and Phase 2 patients at the RP2D). Within Group A and Group B, patients treated at doses other than RP2D will be summarized separately by study treatment (dose). Within Group B, the patients enrolled in Phase 2 will also be summarized separately for efficacy analyses.

Objective response is defined as a CR or PR per RECIST v.1.1 from the date of first dose of study treatment until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Otherwise, the patient will be counted as a non responder in the assessment of ORR. ORR is defined as the proportion of patients with a confirmed CR or confirmed PR per Investigator's assessment according to RECIST v.1.1. The CR rate is the proportion of patients with CR.

Disease Control (DC) is defined as objective response (CR or PR) or stable disease (SD) per RECIST v.1.1 from the date of first dose of study treatment until disease progression or death due to any cause. The DC rate (DCR) is the proportion of patients with DC.

PFS is defined as the time from the date of first dose of study treatment to the date of disease progression by RECIST v.1.1 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 new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments 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 in which case the death will be considered an event.

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.

DR is defined for patients who have confirmed objective response as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective disease progression or to death due to any cause, whichever occurs first.

TTR is defined for patients who have confirmed objective response as the time from the date of first dose of treatment to first documentation of objective tumor response (CR or PR).

PFS, OS, and DR will be analyzed by the Kaplan-Meier method while TTR will be summarized with descriptive statistics. Best overall response (BOR) will be summarized, and ORR and DCR will be calculated along with the corresponding exact 2-sided 95% confidence intervals. For Group B Phase 2 patients, the CR rate will also be calculated along with the corresponding exact 2-sided 95% confidence interval. CCI [redacted]

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetic Analysis of Crizotinib, PF-06463922, and Avelumab

Standard plasma PK parameters for crizotinib and PF-06463922 will be estimated using non-compartmental analysis. For crizotinib and PF-06463922, standard PK parameters will include maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve during the dosing interval time course (AUC_{tau}), area under the concentration-time curve from time of dosing to the last collection time point (AUC_{last}), trough plasma concentration (C_{trough}), apparent plasma clearance (CL/F), and apparent volume of distribution (V/F), if data permit. Dose-normalized parameters (eg, CDN-C_{max}, DN-AUC) will be reported as appropriate.

For PF-06260182, standard PK parameters will include C_{max}, T_{max}, C_{trough}, metabolite to parent ratio for area under t, he plasma concentration versus time curve during the dosing interval time course (MRAUC.), and the metabolite to parent ratio for C_{max} (MRC_{max}). Descriptive statistics for the PK parameters for crizotinib and PF-06260182 and PF--06463922 will be provided by dose, cycle, and day of assessment in tabular form.

Crizotinib, PF-06260182, and PF-06463922 plasma concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by dose, cycle, day and nominal time. Individual patient and median profiles of crizotinib, PF-06260182, and PF-06463922 concentration-time data will be plotted by dose, cycle and day using nominal times. Median crizotinib, PF-06260182, and PF-06463922 profiles will be presented on both linear-linear and log-linear scales.

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

Crizotinib and PF-06463922 at steady state when combined with avelumab will be compared to PK of crizotinib and PF-06463922 when administered alone in a similar patient population from historical data.

9.5.1.2. Immunogenicity Assessment

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be summarized by dose and overall incidence. For patients with positive ADA or neutrolizing antibodies, the magnitude (titer), time of onset, and duration of ADA or neutrolizing antibodies response will also be described, if data permit.

Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

9.5.1.3. Population Pharmacokinetic Analysis

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 exposure and biomarkers, efficacy endpoints, or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.5.2. Biomarkers

Biomarkers will be assessed separately for whole blood, serum, plasma, archival tumor tissue, and *de novo* tumor tissue biospecimens. In each case, summaries of baseline levels, changes from baseline (where appropriate), expression and genetic alterations will be reported. For continuous variables, summary statistics may include the mean, ratio to baseline, standard deviation, 25th, median, and 75th quartile, %CV and minimum/maximum levels of biomarker measures; for categorical variables, summary may include number and percentage, odds ratio, frequency statistics, as appropriate.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

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9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint will be based on the DLT-evaluable analysis set. All other summaries and analyses of safety parameters will be based on the safety analysis set. Safety data will be summarized by dose level using appropriate tabulations and descriptive statistics (pooling together patients treated at the MTD from both phases of the study).

9.6.1. Analysis of the Primary Endpoint

Dose-Limiting Toxicity (DLT) is the primary endpoint of the study Phase 1b portion. The occurrence of DLTs during the first 2 cycles of treatment, as well as during the anytime throughout the trial in determining the RP2D, observed in the dosing cohorts is used to estimate the MTD as described in the STUDY DESIGN section (Section 3). Adverse Events constituting DLTs will be listed per dose level.

9.6.2. Analysis of Secondary Safety Endpoints

The Safety Analysis Set will be used for all secondary safety evaluations. Summaries of AEs and other safety parameters will be presented separately for Group A (including Phase 1b and Phase 2 patients at the RP2D) and Group B at the RP2D. Within Group A and Group B, patients treated at doses other than RP2D will be summarized separately by study treatment (dose).

Adverse Events

AEs will be graded by the investigator according to the CTCAE v4 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. These summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles >1).

Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE v4 severity grade whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test.

The analyses will summarize laboratory test results both on the entire study period and by cycle (Cycle 1 and Cycles >1).

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory abnormalities.

Electrocardiograms

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline corrected QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment. Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

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9.8. Data Monitoring Committee

An external Data Monitoring Committee will not be established for this study. For the purpose of this protocol, Pfizer procedures for periodic safety review will be applied by an internal safety review team with medical and statistical capabilities to review individual and summary data collected in the safety and clinical databases. Procedures will include surveillance for SAEs according to regulatory guidelines.

Discussions between the investigators and the sponsor of AEs and laboratory abnormalities seen at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and make a benefit/risk assessment to decide if further patient enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients’ personal data consistent with applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent document(s) used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative/parent(s) or legal guardian, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study patients before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application (CTA)) and ethics application

in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as Last Patient Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab, crizotinib and/or PF-06463922 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the Investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year

of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations and Term Definitions

Abbreviation	Term
Ab	Antibody
ACRIN	American College of Radiology Imaging Network
ADA	anti drug antibodies
AE	adverse event
ADCC	Antibody-dependent cellular cytotoxicity
AIDS	acquired immunodeficiency syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
C	Cycle
C	Concentration
CDS	core data sheet
CHF	congestive heart failure
CI	confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CNS	central nervous system
CR	complete response
CRR	Complete Response Rate
CRF	case report form
CRM	Continuous Reassessment Method
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D	Day
DL	Dose level
DLI	Donor Lymphocyte Infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid

Abbreviation	Term
DR	Duration of Response
EC	ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
Eg	for example
EGFR	epidermal growth factor receptor
EFS	Event-Free Survival
EML4	echinoderm microtubule-associated protein-like-4
Etc	'and other things' or 'and so forth'
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GnRH	gonadotropin-releasing hormone agonist
GVHD	graft versus host disease
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
Ie	that is
IND	investigational new drug application
INR	international normalized ratio
irAE	immune-related adverse events
IRB	institutional review board
CCI	[redacted]
CCI	[redacted]
[redacted]	[redacted]
IRT	Interactive Response Technology

Abbreviation	Term
IUD	intrauterine device
IV	Intravenous
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LFT	liver function test
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mTPI	modified toxicity probability interval
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N/A	not applicable
nAB	Neutralizing Antibodies
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OR	Overall Response
ORR	Objective Response Rate
OS	overall survival
pT	target probability
PCD	primary completion date
PD	progressive disease
PD-1	programmed death receptor-1
PD-L1	Programmed death ligand 1
PET	positron emission tomography
PFS	Progression-Free Survival
P-gp	P glycoprotein
PK	Pharmacokinetics
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q	every
QD	every day
ORR	Objective response rate
QT	time between the start of the Q wave and the end of the T wave
R	Ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SC	Subcutaneous
SD	Stable disease
SPC	Summary of Product Characteristics
SRSD	single reference safety document
SST	serum separator tube
T	Time
$T_{1/2}$	terminal elimination half-life
TCR	T-Cell receptor
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TTP	time to progression
ULN	upper limit of normal
UPM	unit probability mass
US	United States
USPI	United States Package Insert
V	volume of distribution
WBC	white blood cell count

Appendix 2. ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3. RECIST Version 1.1

The determination of antitumor efficacy during this study will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation.

Measurability of Tumor Lesions

At baseline, individual tumor lesions will be categorized by the Investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumor lesion: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin, or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the

measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Definitions of Tumor Response

Target Lesions

Complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR) is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (PD) is defined as a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (CR) is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD is defined as a persistence of ≥1 non-target lesions.

Progressive disease (PD) is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Determination of Tumor Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in the following table.

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

[1] Measurable lesions only.
[2] May include measurable lesions not followed as target lesions or non-measurable lesions.
[3] Measurable or non-measurable lesions.

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment. It should also be noted that a tumor marker increase does not constitute adequate objective evidence of tumor progression. However, such a tumor marker increase should prompt a repeat radiographic evaluation to document whether or not objective tumor progression has occurred.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy before confirming the complete response status.

Appendix 4. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 4.03, dated 14 June 2010) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

- [redacted]
- [redacted]

CCI [redacted]

CCI [redacted]

- [redacted]
- [redacted]

CCI

CCI

CCI

Lesions

CCI

Appendix 6. Drugs Known to Prolong PR Interval

The following are examples and should not be considered all-inclusive listing.[54]

Drug	Action	Indications
Affecting AV nodal conduction (PR interval)		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyarmide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-1 protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		
Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT3 receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial