CLINICAL PROTOCOL

A PHASE 1B, OPEN LABEL, DOSE ESCALATION STUDY TO EVALUATE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AXITINIB (AG-013736) IN COMBINATION WITH CRIZOTINIB (PF-02341066) IN PATIENTS WITH ADVANCED SOLID TUMORS

Compounds:	AG-013736, PF-02341066
Compound Names:	axitinib, crizotinib
United States (US) Investigational New Drug (IND) Numbers:	IND 63,662 IND 73,544
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Phase:	1b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	26 January 2016	Added EudraCT number. SCHEDULE OF ACTIVITIES: - Contraception check added to align with the Sponsor's most recent protocol template. - Registration and Study Treatment: updated to clarify which patient subgroup will receive axitinib single agent during a 7-day Lead-In period and which subgroup will start with the combination without the Lead-In period. - Archival Tumor Tissue, De Novo Tumor Biopsy: footnotes updated to align with Patient Selection Section, Inclusion Criterion #1. Section 1. Introduction: literature updated; axitinib and crizotinib safety data updated according to the last version of the Investigator's Brochure. Section 4. Patient Selection: - Inclusion Criterion #1, Dose Expansion Phase: language updated: 1. to make the selected patient population more in line with the actual 2nd and 3rd line advanced RCC population; 2. to include alternative option for the collection of biopsy in the Dose Expansion Cohort 2 patients. - Exclusion Criterion #8: language updated to align with the current standard language of crizotinib clinical protocols. PK wording: whenever needed, the wording was updated to clarify that PK samples will be collected in at least 8 evaluable patients in the Expansion Phase Cohort 1. The protocol wording (including pregnancy, contraception, AE Reporting, and publication of study results) and

		sections numbering were updated according to the Sponsor's most recent protocol template. The protocol language (including renal cyst monitoring, overdose instructions, concomitant medications, ophthalmology examinations) was updated according to the current standard language of crizotinib and axitinib clinical protocols.
Amendment 1	11 March 2014	SCHEDULE OF ACTIVITIES: - Frequency of hepatic laboratory test monitoring and relevant footnote modified in accordance with the Dear Investigator Letter dated 23Oct2013. - Follow Up for dosing compliance: added recommendation to follow up for dosing compliance also whenever there is a dose change. - Tumor Assessments: footnote updated to be consistent with Section 7.5. Tumor Response Assessments - Home blood pressure monitoring, pulse rate: frequency and relevant footnote updated to clarify it has to be monitored starting from patient registration. - Archived tumor tissue: footnote updated to be consistent with Section 4. Patient Selection. Section 4. Patient Selection: - Inclusion Criteria #1: language updated to clarify the collection of archival tumor tissue in the Dose Escalation Phase. - Inclusion Criteria #10: language about legal representative deleted in accordance with Western Institutional Review Board request. - Inclusion Criteria #8, Exclusion Criteria #2, and Exclusion Criteria #7: language updated to clarify the criteria. Section 5.3.2.2. Dose Modifications in Case of Drug-Related Toxicity – Table 5: - Management of bradycardia modified in accordance with the recently updated crizotinib Core Data Sheet.

		Section 5.3.5. Compliance: added recommendation to perform follow up by telephone whenever there is a dose change. Section 5.5.4. Other Concomitant Medications: - Language on concomitant use of anticoagulants updated. - Language on concomitant use of bradycardia inducing agents updated. Section 6.1.1. Archival Tumor Tissue: language updated to be consistent with Section 4. Patient Selection. Section 7.1.6. Ophthalmologic Examinations and Section 9.6.4. Ophthalmologic Data: language updated to clarify optional tests to be done based on clinical judgement. Section 7.5 Tumor Response Assessments: language updated to be consistent with the Schedule of Activities Section 12.3. Patient Information and Consent: language about legal representative deleted in accordance with Western Institutional Review Board request.
Original protocol	10 July 2013	Not Applicable (N/A)

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

Background and Rationale:

Until 2005, interferon-alpha (IFN-α) and high dose interleukin (IL)-2 cytokine-based therapies were the conventional treatments for patients with advanced renal cell cancer (RCC), but efficacy was modest. Since then, multiple vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors have supplanted cytokines as the cornerstone of therapy. VEGF inhibitors include VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) axitinib, sunitinib, pazopinib, and sorafenib, and the monoclonal anti-VEGF antibody bevacizumab.

Despite the success of these anti-angiogenic therapies in multiple treatment settings including RCC, a fraction of patients are refractory to VEGF inhibitors, and the majority of patients will eventually develop evasive resistance and exhibit disease progression while on therapy. Nonclinical models suggest that at progression, the resistant tumor is aggressive both locally and at distant metastatic sites. Several mechanisms have been proposed to explain these phenomena. Recent data support a significant role for the membrane receptor tyrosine kinase mesenchymal-epithelial transition factor (c-MET) and its ligand hepatocyte growth factor (HGF) (or scatter factor) in tumor resistance to VEGF inhibitors.

It is therefore proposed that combining a c-MET inhibitor with a VEGF inhibitor will provide clinical benefit compared to treatment with a VEGF pathway directed therapy alone. This supports the testing of crizotinib, as c-MET inhibitor, in combination with the VEGFR inhibitor axitinib. Since this will be the first study of axitinib given in combination with crizotinib, the primary objective of the study will be the assessment of the safety and tolerability of the combination regimen. However, once the tolerability of the combination has been confirmed, its antitumor activity will be preliminarly assessed in advanced RCC expansion cohorts in both the first line setting, and second/third line setting following disease progression on a VEGF pathway inhibitor. This will explore the activity of the combination in both preempting the development of resistance to VEGF pathway inhibitor and in treating tumors already resistant to VEGF pathway inhibitor.

Objectives and Primary Endpoint:

Primary Objective

- To assess the safety and tolerability of axitinib in combination with crizotinib in patients with solid tumors and advanced RCC in order to estimate the maximum tolerated dose (MTD) (or Maximum Feasible Dose [MFD]) and select the recommended Phase 2 dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile.
- To characterize the pharmacokinetics (PK) of axitinib and crizotinib when administered in combination and to assess the effect of crizotinib on the PK of axitinib (Dose Escalation Phase and at least 8 PK-evaluable subjects in Expansion Phase Cohort 1 only).
- To characterize the effects of axitinib in combination with crizotinib on QTc.
- To document the anti-tumor activity of axitinib in combination with crizotinib in advanced RCC patients.
- To explore the pharmacodynamic effect of axitinib in combination with crizotinib in blood.
- To characterize the alterations and/or expression profiles of genes, proteins, and RNAs relevant to angiogenesis (eg, Ang-2), drug targets (eg, c-MET) and sensitivity and/or resistance (eg, PBRM1) to axitinib in combination with crizotinib in tumor and/or blood.

The primary endpoint of the study is first-cycle dose limiting toxicities (DLTs).

Study Design:

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of axitinib in combination with crizotinib in adult patients with advanced solid tumors. This clinical study will be composed of a Dose Escalation Phase and a Dose Expansion Phase. The Dose Escalation Phase will estimate the MTD in dose escalation cohorts in patients with advanced solid tumors, using the modified toxicity probability interval (mTPI) method.

The Dose Escalation Phase will lead to the identification of an Expansion Test Dose for axitinib in combination with crizotinib in patients with solid tumors. The Expansion Test Dose will be either the MTD or the MFD, ie, the highest tested dose that is declared safe and tolerable by the Investigators and Sponsor. Once the Expansion Test Dose is identified, the Dose Expansion Phase will be opened and axitinib in combination with crizotinib will be tested in patients with advanced RCC.

The Dose Expansion Phase is comprised of two patient populations, both with histologically or cytologically confirmed advanced RCC with a component of clear cell subtype and:

- Cohort 1: No prior systemic therapy directed at advanced RCC.
- Cohort 2: At least one but no more than two prior systemic treatment regimens directed at advanced RCC, with at least one prior therapy being a regimen containing an approved VEGF-pathway inhibitor, and resistance to the most recently received approved VEGF-pathway inhibitor. Resistance is defined as disease progression as per RECIST version 1.1 while on treatment with a VEGF-pathway inhibitor.

To understand the PK effects of crizotinib on axitinib, a 7-day lead-in period of single-agent axitinib directly preceding the administration of the crizotinib and axitinib combination will be included prior to Cycle 1 in the Dose Escalation Phase of the study. Axitinib is not expected to affect crizotinib exposure so there will be no PK study with a lead-in period of single-agent crizotinib. The Dose Expansion Phase Cohort 1 will be used to further study crizotinib and axitinib PK interactions in at least 8 evaluable patients; in this cohort, the PK profile for axitinib single agent during the 7-day lead-in period will be compared to that of axitinib in combination with crizotinib during Cycle 1. No lead-in period will be included in the Dose Expansion Phase Cohort 2.

Anti-tumor activity will be evaluated every 8 weeks after Cycle 1 Day 1 using RECIST version 1.1. Given the safety profile of crizotinib, in addition to standard safety tests, ophthalmology examinations will be carried out to assess any vision changes. Based on the safety profile of axitinib, blood pressure will be monitored throughout the treatment period, as well as thyroid function.

Electrocardiogram (ECG) measurements will be taken throughout the treatment period in all patients and in conjunction with PK sampling in patients from the Dose Escalation Phase and the Dose Expansion Phase Cohort 1. Archived tumor tissues will be collected for all patients. De novo tumor biopsy will be collected for the patients in the Dose Expansion Phase Cohort 2. For all patients a second biopsy might be provided on a voluntary basis at the time of disease progression. Biomarker studies on tumor tissue and blood will be carried out to help understand the mechanism of action of the axitinib plus crizotinib combination, as well as potential mechanisms of resistance. Such results may help in the future development of this combination. These analyses may also result in the identification of potential biomarkers of response to the axitinib plus crizotinib combination, ultimately leading to development of a patient selection strategy for further clinical investigation. As such collection and analysis of the archival tumor tissue as well as de novo tumor biopsies at baseline and at time of progression will be paramount to generate such knowledge.

Up to 65 patients are expected to be enrolled in the study.

Study Treatment:

Crizotinib and axitinib will be given orally (PO) twice daily (BID) on a continuous dosing schedule in 28-day cycles. Treatment with study drugs will continue until disease progression, patient refusal, patient lost to follow up, or unacceptable toxicity occurs, or the study is terminated by the Sponsor. Patients with unacceptable toxicity attributed to one of the two drugs may be eligible for continued treatment with the other drug (after discussion between the Investigator and the Sponsor). Patients with disease progression but who are still experiencing clinical benefit will be eligible for continued treatment with single agent axitinib or axitinib combined with crizotinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Statistical Methods:

Up-and-Down Matrix Design with the mTPI Method

The escalation/de-escalation rules will follow the modified toxicity probability interval (mTPI) method[38] (see Section 9.2 and Appendix 5). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level) to determine where future cohorts should involve dose escalation, no change in dose, or dose de-escalation.

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

- The target enrollment cohort size is 3 patients. The first 3 patients treated in Dose Level 1 cohort will initiate dosing sequentially, at least 2 days apart to allow for the initial evaluation of toxicities and tolerability. If there are no safety concerns, any additional patients enrolled to this dose cohort will not be required to initiate dosing sequentially.

- The next cohort can be enrolled when all patients at the current dose cohort have been evaluated for 28 days (ie, the first treatment cycle), or experience a dose limiting toxicity (DLT), whichever comes first.

- If a patient withdraws from the study before receiving at least 75% of the planned first-cycle dose of both axitinib and crizotinib for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.

- The dose-finding component of the trial is completed when at least 10 evaluable patients have been treated at the highest dose associated with a DLT rate <0.33. It is estimated that approximately 25 DLT evaluable patients will need to be enrolled to reach 10 DLT-evaluable patients at the estimated MTD.

- The proposed doses, schedule and PK timepoints may be reconsidered and amended during the study based on the emerging safety and PK data.

- The RP2D will be confirmed in the Dose Expansion Phase, taking into account the MTD/MFD determination from the Dose Escalation Phase, and other factors related to safety, efficacy, and PK/PD involving all available data from tests cohorts.

Sample Size Determination

Due to the dynamic nature of the cohort allocation procedure used in this study, the sample size of the Up-and-Down matrix design using the mTPI approach cannot be determined in advance. It is estimated that 25 DLT evaluable patients will be enrolled in the Dose Escalation Phase in order to have a reliable and accurate estimate of the MTD. The two expansion cohorts will enroll up to 20 response evaluable patients each at the estimated MTD or MFD.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table (SOA) provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments (Sections 6 and 7 of the protocol, respectively) for detailed information on each procedure and assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed on the Schedule of Activities, in order to conduct evaluations or assessments required to protect the wellbeing of the patient.

SCHEDULE OF ACTIVITIES

Protocol Activities[1]	Screening	Lead-in PK Period[2]		Study Treatment (1 cycle = 28 days)				Post Treatment	
				Cycle 1			Cycles ≥2		
	≤28 Days Prior to Registration	Day 1 (±2 days)	Day 7	Day 1 (±3 days)	Day 3 (+3 days)	Day 15 (±3 days)	Day 1 (±3 days)	End of Treatment /Withdrawal (±3 days)[3]	Follow-up Day 28 (+7 days) after Last Dose[4]
Documentation									
Informed Consent[5]	X								
Medical/Oncological History [6]	X								
Baseline Signs/Symptoms[7]		X		X					
Physical Examination [8]	X			X		X	X	X	
ECOG Performance Status	X	X		X		X	X	X	
Blood Pressure, Pulse Rate[9]	X	X	X	X		X	X	X	
Home Blood Pressure Monitoring, Pulse Rate [10]		----------X----------							
Ophthalmologic Examination[11]	X	----------At the first occurrence of any vision changes and as clinically indicated----------							
Follow-up for Dosing Compliance [12]					X (and whenever there is a dose change)				
Laboratory Studies									
Hematology[13]	X	(X)		X		X	X	X	
Blood Chemistry[13]	X	(X)		X		X	X (LFTs also on Cycle 2 Day 15)	X	
Coagulation[13]	X	(X)		X		X	X	X	
Urinalysis[14]	X	(X)		X		X	X	X	

Protocol Activities[1]	Screening	Lead-in PK Period[2]		Study Treatment (1 cycle = 28 days)				Post Treatment	
				Cycle 1			Cycles ≥2		
	≤28 Days Prior to Registration	Day 1 (±2 days)	Day 7	Day 1 (±3 days)	Day 3 (+3 days)	Day 15 (±3 days)	Day 1 (±3 days)	End of Treatment /Withdrawal (±3 days)[3]	Follow-up Day 28 (+7 days) after Last Dose[4]
12-lead ECG[15]	X			X		X	X (Cycles 2 and 3)	X	
Thyroid Function Tests [16]	X	(X)	X	X		X	X		
Pregnancy Test [17]	X	X		X			X	X	
Contraception check[18]	X	X		X			X	X	
Disease Assessments									
Tumor Assessments (including scans)[19]	X			X Every 8 weeks (±7 days) from Cycle 1 Day 1				X	
Other Clinical Assessments									
Adverse Events[20]		----------X----------							
Concomitant Medications/Treatments[21]	X	(X)	X	X		X	X	X	X
Registration and Study Treatment [22] - Escalation Phase and Expansion Phase Cohort 1 (patients with PK sample collection)									
Crizotinib				----------X (twice daily) ----------					
Axitinib		----------X (twice daily) ----------							
Registration and Study Treatment [22] - Expansion Phase Cohort 1 (patients with no PK sample collection) and Expansion Phase Cohort 2									

Protocol Activities[1]	Screening	Lead-in PK Period[2]		Study Treatment (1 cycle = 28 days)				Post Treatment	
				Cycle 1			Cycles ≥2		
	≤28 Days Prior to Registration	Day 1 (±2 days)	Day 7	Day 1 (±3 days)	Day 3 (+3 days)	Day 15 (±3 days)	Day 1 (±3 days)	End of Treatment /Withdrawal (±3 days)[3]	Follow-up Day 28 (+7 days) after Last Dose[4]
Crizotinib				----------X (twice daily) ----------					
Axitinib				----------X (twice daily) ----------					
Other Samplings									
Pharmacokinetics[23]			X			X	X (Cycles 2-5)		
Plasma Biomarkers[24]		X		X		X	X (Cycles 2, 3 and 5)	X	
Serum Biomarkers[25]	X						X (Cycle 2)	X	
Banked Biospecimen[26]	X								
Archival Tumor Tissue [27]	X								
De Novo Tumor Biopsy[28]	X							X (optional)	

Footnotes for Schedule of Activities
1. **Protocol Activities:** All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. Patients will visit site at: Screening, Lead-in Day 1, Lead-in Day 7, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and all subsequent Cycles at Day 1, End of Treatment and Follow-up Day 28 after last dose.
2. **Lead-in PK Period:** Dose Escalation Phase, and Dose Expansion Phase Cohort 1.
3. **End of Treatment/Withdrawal:** Obtain these assessments ±3 days of End of Treatment/Withdrawal if not completed in the last week, except for tumor assessment which need not be repeated if performed within the prior 8 weeks.
4. **Follow-up Day 28 after last dose:** To occur at least 28 days, and no more than 35 days, after discontinuation of treatment.
5. **Informed Consent:** Must be obtained prior to undergoing any trial specific procedure.
6. **Medical/Oncological History:** To include information on prior systemic therapy regimens, surgery and radiation therapy; and for Dose Expansion Phase Cohort 2, to include documentation showing disease progression according to RECIST (version 1.1).

7.	**Baseline Signs/Symptoms:** To be documented and recorded at Lead-in Day 1 (predose) for patients in Lead-in, at Cycle 1 Day 1 (predose) for all other patients.
8.	**Physical Examination:** Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at screening only).
9.	**Blood pressure, pulse rate:** 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. Two blood pressure readings will be taken at least 1 hour apart at each clinic visit.
10.	**Home blood pressure monitoring, pulse rate:** when patients are registered, they will receive home blood pressure monitoring devices to monitor blood pressure and pulse at home. Patients taking axitinib (as single agent during the Lead-in, or combined with crizotinib) will monitor their blood pressure at least twice daily (before taking each dose of axitinib) and blood pressure should be recorded in a patient diary. Patients should be instructed to contact the site immediately for guidance if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance) although a different blood pressure threshold for contacting the site may be used according to the Investigator's clinical judgment (see Section 5.3.2.3). It's also important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.
11.	**Ophthalmologic Examination:** Includes visual acuity fundoscopy, and slit lamp and should be performed by an ophthalmologist. The ophthalmologic examination should be repeated during the study when AE vision disorders are first observed or worsen from previous visit (see Section 7.1.6).
12.	**Follow-up for Dosing Compliance:** Follow-up by telephone will be done on Cycle 1 Day 3 (+ 3 days) to confirm patient understanding and compliance with dosing instructions. If needed, patient will be retrained. The follow-up for dosing compliance by telephone is recommended also whenever there is a dose change.
13.	**Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 6. Liver function tests (LFTs) (including transaminases and total bilirubin) have to be monitored every 2 weeks during the first 2 cycles of treatment, then once per cycle and as clinically indicated. LFTs should be measured more frequently in the event of Grade 2-4 elevations or signs or symptoms consistent with hepatotoxicity.
14.	**Urinalysis (**Table 6): If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein will have to be quantified by 24 hour urine collection. Dose adjustment may be required (see Section 5.3.3.2). Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein.
15.	**12-lead ECG**: See Section 7.1.5 for details. Single ECG measurement will be obtained at screening. Triplicate ECG measurements will be measured approximately 2 minutes apart on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 3 Day 1. One set of triplicate ECGs will be measured pre-dose (prior to study drug morning dose) at each of these clinic visits and a second set of triplicate ECGs will be measured 2-6 hours post that day's morning crizotinib dosing. If the mean QTc interval is prolonged (≥501 msec), then the ECG should be read by a cardiologist at the site for confirmation. Additional ECGs will be performed as clinically indicated.
16.	**Thyroid function tests:** Free T3, free T4 and TSH will be performed at Lead-in Day 1 and Lead-in Day 7 (for patients in Lead-in); at baseline (Cycle 1 Day 1 pre-dose or within 7 days of Cycle 1 Day 1) for all patients. Subsequently, TSH should be assessed at Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, Cycle 4 Day 1, and every 8 weeks thereafter starting from Cycle 6 Day 1. Free T3 and free T4 should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state.

17. **Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study treatment: once at the start of screening (all patients), and once at Lead-in Day 1 (patients in Lead-in) immediately before axitinib administration, or at the baseline visit (all other patients) immediately before the administration of axitinib in combination with crizotinib. Following a negative pregnancy test 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. Pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study treatment and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken as per request of IRB/IECs or if required by local regulations (see Section 7.1.1).
18. **Contraceptive 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.
19. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans; brain CT or MRI scan for patients with suspected brain metastases. The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, and then every 8 weeks from Cycle 1 Day 1 of combination treatment, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 8 weeks). For patients with known or suspected bone metastases a bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT is required at screening. Repeat bone imaging is required 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 confirmation of response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1.
20. **Adverse Events:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. The AE reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last investigational product administration. SAEs experienced by 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 Case Report Form (CRF) from the time the patient has taken at least one dose of study treatment through last patient visit (Day 28 after last dose). 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.
21. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non drug supportive interventions (eg, transfusions).
22. **Registration:** Patient number and dose level allocation operated by Pfizer Inc. Required information: site and patient identifiers and demographic information. Study treatment (either single agent axitinib for patients in Lead-in or axitinib in combination with crizotinib for all other patients) should begin within 7 days of registration.
    Study Treatment: Axitinib and crizotinib will be given twice daily PO on a continuous schedule. Axitinib in combination with crizotinib will be given every 28 days (28 days = 1 cycle) (see Section 5).

23. **Pharmacokinetics**: Samples will be collected at the time points indicated in the Pharmacokinetic Sample Table. Pharmacokinetic samples will be collected from all patients in the Dose Escalation Phase. For the Dose Expansion Phase, pharmacokinetic samples will be obtained from at least 8 evaluable patients in Cohort 1 only.
24. **Plasma Biomarkers**: Blood samples (10 mL) will be obtained to measure DNA, RNA or protein markers known or suspected to be of relevance to the mechanism of action, the development of resistance or the identification of those patients who might benefit from treatment with axitinib in combination with crizotinib. Blood samples will be collected pre-dose at either Lead-in Day 1 (patients in Lead-In) or Cycle 1 Day 1 (patient with no Lead-In) before first dose, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 5 Day 1. The End of Treatment blood sample should be obtained during the End of Treatment visit, at the time of disease progression. See Section 7.3.2.
25. **Serum Biomarkers**: Blood samples (10 mL) will be obtained to measure DNA, RNA or protein markers known or suspected to be of relevance to the mechanism of action, the development of resistance or the identification of those patients who might benefit from treatment with axitinib in combination with crizotinib. Blood samples will be collected at screening, Cycle 2 Day 1 predose, and during the End of Treatment visit, at the time of disease progression. See Section 7.3.2.
26. **Banked Biospecimen:** Where local regulations allow, a single 4 mL blood sample will be collected at screening and retained in a biobank for possible analysis of DNA sequence variation in genes that may affect the PK of the study drugs (eg, genotyping of drug metabolizing enzymes and transporters), that may be associated with specific adverse events or toxicities, or that may correlate with efficacy. See Section 7.4.
27. **Archival Tumor Tissue:** All patients will provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen, or, if not available, a de novo tumor biopsy must be obtained for this purpose in accordance with local institutional practice for tumor biopsies. For patients in the Dose Escalation Phase, the archival tumor tissue can be from either initial diagnosis or recurrence or metastatic site. For patients in the Dose Expansion the archival tumor tissue must be from the initial diagnosis. Formalin fixed, paraffin embedded (FFPE) tissue block of archival tumor tissue that contains sufficient tissue to generate at least 12 unstained slides, each with tissue sections that are 5 microns thick, will be collected. If no FFPE block is available, then at least 12 unbaked and unstained slides containing FFPE tissue sections, that are 5 microns thick must be provided. See Section 7.3.1.
28. **De Novo Tumor Biopsy:** Mandatory for all patients enrolled in Dose Expansion Phase Cohort 2. This de novo biopsy must be taken no more than 28 days prior to registration. Alternatively, a recently obtained FFPE tumor tissue block from a resection or biopsy of a primary, recurrent or metastatic lesion can be provided if the following criteria are met: 1) the biopsy or resection was performed within 4 months of study start AND 2) the patient has not received any new intervening systemic anti-cancer treatment from the time the tissue was obtained and the study start. Any patient enrolled into the Dose Expansion Phase Cohort 1 or into the Dose Escalation Phase may provide a de novo biopsy on a voluntary basis. For those patients, this sample will be provided in addition to the archival tumor tissue that is required for enrollment, unless archived tumor tissue is not available in which case the de novo biopsy is mandatory. In addition, a de novo tumor biopsy is encouraged on or around the End of Treatment visit, eg, at the time of disease progression, from all patients. The de novo biopsy will consist of an incisional or excisional biopsy, or a core needle biopsy, of a primary or metastatic site. Fine needle aspiration biopsies are not acceptable. The tumor biopsy will be processed as specified in the Laboratory Manual. See Section 7.3.1.

(X) = only if activity not performed in prior 7 days.

PHARMACOKINETIC SAMPLES – DOSE ESCALATION PHASE AND DOSE EXPANSION PHASE COHORT 1

Axitinib	Axitinib in Combination with Crizotinib	
Lead-in Day7[a] (PK sample for axitinib)	**Cycle 1 Day 15[b] (PK sample for axitinib and crizotinib)**	**Cycle 2 – Cycle 5, Day 1[c] (PK sample for crizotinib)**
Predose	Morning Predose	Morning Predose
1 hr postdose	1 hr postdose	
2 hr postdose	2 hr postdose	
3 hr postdose	3 hr postdose	
4 hr postdose	4 hr postdose	
6 hr postdose	6 hr postdose	
8 hr postdose	8 hr postdose	

PK: pharmacokinetics

Note: PK in Dose Expansion Phase Cohort 1 will be collected in at least 8 evaluable patients. Dose Expansion Phase Cohort 2 will not receive lead-in dosing or require any PK samples to be taken.

[a] One sample (3 mL) collected at each time point for axitinib.

[b] Two samples (3 mL each) collected at each time point; one for axitinib and one for crizotinib.

[c] One sample (3 mL) collected for crizotinib.

1. INTRODUCTION

1.1. Indication

Axitinib in combination with crizotinib is indicated for the treatment of advanced solid tumors (Dose Escalation Phase) and de novo or VEGF inhibitor pretreated advanced renal cell cancer (RCC) patients (Dose Expansion Phase).

1.2. Background and Rationale

1.2.1. Tumor Angiogenesis and VEGF-Pathway Inhibition

Tumor angiogenesis is a complex dynamic process necessary for the continued growth of solid tumors. VEGF is one of the most important angiogenic factors secreted by the tumor and other cells. Its production is enhanced by several stimuli, including hypoxia. VEGF and VEGF receptors (VEGFRs) are critical components of the processes leading to the branching, extension, and survival of endothelial cells which form new blood vessels during angiogenesis, and which is an absolute necessity for tumor growth beyond microscopic size. Inhibitors of angiogenesis are now widely used in the treatment of cancer and most of these agents inhibit the VEGF pathway. VEGF inhibitors include the VEGFR TKIs axitinib, sunitinib, pazopanib, and sorafenib, and the monoclonal anti-VEGF antibody bevacizumab. VEGF inhibitors have been approved in a number of indications, including the treatment of RCC.[1,2]

1.2.2. Renal Cell Cancer

An estimated 65,150 new cases of kidney cancer are expected to be diagnosed in the United States of America (US) in 2013. This includes 93% RCC, 6% renal pelvis cancer and 1% Wilms tumor. An estimated 13,680 patients will die from kidney cancer in 2013.[3]

RCC arises from the renal epithelium and 5 major subtypes are currently recognized. Approximately 70-80% of these are clear cell RCC tumors while other less common cell types include papillary (Type I and II), chromophobe, collecting duct and unclassified RCC.[4] Four RCC predisposing genes have been identified – *MET* protooncogene, von Hippel-Lindau tumor suppressor gene (*VHL*), fumarate hydratase tumor suppressor gene (*FH*), and Birt-Hogg-Dubé tumor suppressor gene (*BHD*).

Patients with von Hippel-Lindau disease have a >70% risk of developing clear cell RCC. This hereditary form of RCC is caused by germline mutations in the *VHL* tumor suppressor gene on chromosome 3p. More than 90% of sporadic clear cell RCC involves somatic *VHL* gene mutations or methylation. *VHL* gene mutations lead to loss of function of the VHL protein, accumulation of hypoxia-inducible transcription factors (eg, HIF-1alpha and HIF-2 alpha) which translocate to the nucleus and increase transcription of angiogenesis factors (such as VEGF and platelet derived growth factor (PDGF)) which induce tumorgenesis. Clear cell RCC is a highly vascular tumor with high expression of VEGF, VEGFRs and PDGF receptor.[5]

About one-third of patients with clear cell RCC present with Stage IV disease. Systemic therapy is given to patients with advanced disease (relapsed or Stage IV) that is not amenable to complete resection. However, it is recommended that these patients undergo a cytoreductive nephrectomy where possible, prior to beginning systemic therapy, as per treatment guidelines.[6]

There are 7 targeted agents approved in the US as systemic therapy for advanced RCC that is predominantly clear cell. First line systemic therapy is usually one of the VEGFR TKIs (sunitinib, pazopanib, or sorafenib), or the monoclonal anti-VEGF antibody bevacizumab (given in combination with 0) or the mTOR inhibitor, temsirolimus. The same targeted agents or the VEGFR TKI axitinib, or the mTOR inhibitor everolimus are used individually in subsequent lines of therapy for advanced clear cell RCC.[6,7,8,9]

1.2.3. Rationale

1.2.3.1. c-MET and Resistance to Antiangiogenic Therapy

Despite the success of antiangiogenic therapy in multiple treatment settings including RCC, a fraction of patients are refractory to VEGF inhibitor treatment and the majority of patients will eventually develop resistance and exhibit disease progression while on therapeutic regimen.[10,11] Nonclinical studies suggest that anti-angiogenic therapy may have induced the tumor to be more aggressive.[12,13,14] Models show VEGF inhibitor-resistant tumors to be more locally invasive and exhibit enhanced distant metastases. Several mechanisms have been proposed to explain resistance and this increase in tumor aggressiveness. These include activation of pathways that favor epithelial-mesenchymal transition (EMT) such as c-MET; a switch to vasculogenesis; co-option of normal organ vasculature; blood flow alterations due to tumor vessel pruning and normalization; and changes in the dominant VEGF isoform.

Another proposed tumor resistance mechanism involves a switch from VEGF to alternative proangiogenic mediators such as HGF and PDGF. According to this hypothesis, antiangiogenic therapies normalize and reduce tumor vascularization and increase tumor hypoxia. Hypoxia and the overexpression of HIF-1 leads not only to the accumulation of VEGF and PDGF, but also increases HGF expression in tumor and surrounding normal interstitial cells and increases c-MET receptor expression in endothelial and tumor cells. The HGF/c-MET pathway and VEGFR pathway can act synergistically to promote tumor survival. Additionally, HGF has its own role as an independent angiogenic factor and so may substitute, at least in part, for VEGF. Up-regulation of HGF/c-MET signaling increases tumor invasiveness and distant metastasis.[15,16,17]

Nonclinical models support a role for HGF/c-MET in VEGF inhibitor resistance.[17,18] In several tumor models resistant to the VEGF TKI sunitinib, a combination of sunitinib plus the c-MET inhibitor PF-04217903 inhibited tumor growth to a greater degree compared to either inhibitor alone.[19] A similar synergistic action was seen in a later study using sunitinib combined with the c-MET inhibitor crizotinib in both breast and colorectal orthotopic tumor models resistant to sunitinib. Histological analysis suggested that combination treatment mainly targeted the vasculature in resistant tumors. Moreover, exogenous HGF conferred resistance to sunitinib.[20] In a pancreatic neuroendocrine RIP-TAG-2 model, sunitinib

increased hypoxia, expression of HIF-1alpha, c-MET, and markers of EMT. Importantly, invasion and metastasis were prevented when sunitinib was accompanied by concurrent administration of one of the c-MET inhibitors PF-4217903 or crizotinib.[21] A similar benefit was found in orthotopic pancreatic carcinomas treated with cabozantinib (XL184), a receptor TKI that blocks both c-MET and VEGFR2. Cabozantinib prevented or reversed invasiveness, reduced the number and size of liver metastases, and prolonged survival.[22]

Recently, there has been a report of axitinib in combination with crizotinib in two RCC nonclinical models. Human high cMET expressing 786-O and low cMET expressing RP-01 xenograft tumors were treated with vehicle, axitinib, crizotinib, or axitinib combined with crizotinib. Significant synergistic effects were found with crizotinib combined with axitinib with tumor inhibition reported as 17% with axitinib alone compared to 76% with the combination ($P<0.05$).[23]

Taken together, nonclinical data indicate that resistance to VEGF inhibitors is accompanied by intratumoral hypoxia, activation of HIF-1 alpha, an increase in c-MET activity, and EMT. Inhibition of cMET and VEGFR together has synergistic effects on tumor growth, angiogenesis, invasiveness, and metastasis in a number of models.[17,18,19,20,21,22,23] The recently reported synergistic effect between axitinib and crizotinib further suggests that dual targeting of c-MET and VEGF pathways may be effective in RCC.[23]

Further support for combining a VEGFR inhibitor with a c-MET inhibitor comes from the observed clinical activity of cabozantinib. Cabozantinib has demonstrated broad clinical activity in multiple tumor types including medullary thyroid cancer, breast, ovarian, prostate and lung cancers, melanoma, glioblastoma, hepatocellular carcinoma and RCC.[24] A Phase 2 study in 171 patients with castration-resistant prostate cancer (CRPC) reported that 72% of evaluable patients had shrinkage of soft tissue lesions whereas 68% had an improvement on bone scan. The objective response rate (ORR) at 12 weeks was 5% and there was stable disease (SD) in 75% of patients. The observed effects on bone scan are unprecedented and not seen with single agent VEGF-pathway targeted therapy; this suggests that dual targeting of both VEGF and c-MET pathways may lead to improved outcome for patients with CRPC.[25]

Clinical activity of cabozantinib in advanced pretreated RCC has been noted in a Phase I trial and confirmed in the METEOR trial, a randomized Phase 3 trial of cabozantinib versus everolimus in patients with renal cell carcinoma that had progressed after VEGFR-targeted therapy.[26, 42] Progression-free survival (PFS) was longer with cabozantinib than with everolimus, with median PFS 7.4 months with cabozantinib and 3.8 months with everolimus. The risk of progression or death was 42% lower with cabozantinib than with everolimus (hazard ratio, 0.58; 95% confidence interval [CI] 0.45 to 0.75; $P<0.001$). The ORR was 21% with cabozantinib and 5% with everolimus ($P<0.001$). A planned interim analysis showed that overall survival (OS) was longer with cabozantinib than with everolimus (hazard ratio for death, 0.67; 95% CI, 0.51 to 0.89; $P = 0.005$) but did not cross the significance boundary for the interim analysis.[42]

In conclusion, dual targeting of VEGF and c-MET pathways demonstrates significant clinical activity in a number of cancers including RCC. This is consistent with the nonclinical data supporting a role for c-MET in resistance to VEGFR targeted therapy and demonstration of synergy between VEGF pathway inhibition and c-MET inhibition in several models including axitinib in combination with crizotinib in RCC.

1.2.3.2. Hypothesis to be Tested

The above clinical and nonclinical data support the hypothesis that c-MET signaling contributes significantly to VEGF inhibitor resistance such that combining a c-MET inhibitor with a VEGFR inhibitor will provide clinical benefit compared to treatment with a VEGF pathway directed therapy alone.

This supports the testing of crizotinib, as c-MET inhibitor, in combination with the VEGFR inhibitor axitinib. Since this will be the first study of axitinib given in combination with crizotinib, the primary objective of the study will be the assessment of the safety and tolerability of the combination regimen. However, once the tolerability of the combination has been confirmed, its antitumor activity will be preliminarly assessed in advanced RCC expansion cohorts in both the first line setting, and second/third line setting following disease progression on a VEGF pathway inhibitor. This will explore the activity of the combination in both preempting the development of resistance to VEGF pathway inhibitor and in treating tumors already resistant to VEGF pathway inhibitor.

1.2.4. Study Drugs

1.2.4.1. Crizotinib (XALKORI®, PF-02341066) as a c-MET Inhibitor

Crizotinib (XALKORI®, PF-02341066) is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) (actual indication varies according to region/country).[27]

Although, crizotinib is a selective ATP-competitive small-molecule, oral ALK/ROS1 TKI with proven clinical activity in ALK-positive NSCLC patients, it is also an inhibitor of c-MET and its oncogenic variants (eg, c-MET/HGFR mutations).[28,29] Crizotinib demonstrated potent (inhibition constant [K_i] in nM range) concentration-dependent inhibition of c-MET phosphorylation in biochemical kinase assays and cell-based assays using tumor cell lines.[29] Crizotinib also demonstrated antitumor efficacy, including marked cytoreductive antitumor activity, in multiple tumor models implanted in athymic mice that expressed activated crizotinib targets including c-MET/HGF. In all assays, crizotinib was found to be at least as potent, if not more potent, an inhibitor of c-MET compared to ALK. Since clinical studies have demonstrated that crizotinib has activity against ALK, this implies that the level of drug attainable in human plasma would be sufficient enough to also inhibit c-MET.

Clinical evidence for crizotinib inhibition of c-MET comes from the Phase 1 clinical trial (A8081001).[29] Crizotinib has shown pharmacodynamic modulation (increase) of soluble MET (sMET), which is a c-MET pathway-specific plasma biomarker. The increase was time-dependent. These observations are consistent with the effects reported for other c-MET inhibitors including foretinib (XL880) and rilotumumab (AMG102).[30]

In addition, antitumor activity has been seen in a number of patients with amplification in the cMET gene locus detected by FISH *(MET/CEP7* ≥2.2). Two of 4 patients having gastroesophageal cancer with MET amplification (*MET/CEP7* >5) experienced tumor shrinkage of -30% (confirmed PR,) and -16% when treated with crizotinib and PFS was 3.7 and 3.5 months, respectively.[31] A patient with ALK negative, c-MET amplified (*MET/CEP7* >5) non-small cell lung cancer (NSCLC) experienced a tumor shrinkage of -54% (confirmed PR) and a durable response of 10+ months when treated with crizotinib.[32] A patient with glioblastoma multiforme (*MET/CEP7* = 2.8), previously treated with the pan-VEGF inhibitor cediranib, had SD for 6+ months associated with significant tumor shrinkage (-40% by MacDonald criteria) when treated with crizotinib.[33]

Taken together, the nonclinical and clinical data support crizotinib as a potent inhibitor of c-MET and further clinical investigation of this activity is warranted.

Among the 1840 patients with NSCLC treated with single-agent crizotinib 250 mg BID, the most commonly reported treatment-related adverse events (AEs) of any severity grade (reported by ≥20% of patients) in decreasing frequency were VISION DISORDER, Nausea, Diarrhoea, Vomiting, EDEMA, Constipation, ELEVATED TRANSAMINASES, Fatigue, and NEUTROPENIA (event terms written in ALL CAPITALS represent CLUSTERED TERMS which included multiple preferred terms). Among the 172 patients with NSCLC treated with single-agent crizotinib 250 mg BID in the randomized Phase 3 study comparing crizotinib to standard-of-care chemotherapy (pemetrexed or docetaxel), the most common crizotinib-related AEs (reported in ≥20% of patients) of any severity in decreasing frequency were VISION DISORDER, Diarrhoea, Nausea, Vomiting, ELEVATED TRANSAMINASES, Constipation, EDEMA, NEUTROPENIA, Dysgeusia, Decreased appetite, and LEUKOPENIA. Among the 171 patients with NSCLC treated with single-agent crizotinib 250 mg BID in the randomized Phase 3 study comparing crizotinib to standard-of-care chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin), the most common crizotinib-related AEs (reported in ≥20% of patients) of any severity in decreasing frequency were VISION DISORDER, Diarrhoea, Nausea, Vomiting, EDEMA, ELEVATED TRANSAMINASES, Constipation, Fatigue, Dysgeusia, Decreased appetite, NEUTROPENIA, and ABDOMINAL PAIN. The safety profile observed for 153 patients with tumor types other than NSCLC treated with single-agent crizotinib 250 mg BID was similar to that of patients with advanced NSCLC. The most common treatment-related AEs (reported in ≥20% of patients) of any severity grade in decreasing frequencies were Nausea, VISION DISORDER, Vomiting, Diarrhoea, and Fatigue.

Complete information for crizotinib may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.[29] Further information may be found in the crizotinib United States Package Insert (USPI).[34]

1.2.4.2. Axitinib (INLYTA®, AG-013736)

Axitinib (INLYTA®, AG-013736) is an oral, small molecule, TKI selective for VEGFRs 1, 2 and 3 and is approved for the treatment of advanced RCC after failure of one prior systemic therapy (actual indication varies according to region/country).

Axitinib is an adenosine triphosphate (ATP)-competitive inhibitor that binds to the unphosphorylated (non-activated) "DFG-out" conformation of the catalytic domain of a receptor tyrosine kinase. In enzymatic assays, axitinib was found to be highly potent (K_i = 28 picomolar) against the kinase activity of juxta-membrane (JM) domain containing human VEGFR 2 recombinant protein.[35] In additional kinase assays, axitinib showed potent and ATP-competitive inhibition of the VEGFRs 1, 2, and 3 and PDGFR-β, but not other closely-related family kinases. Receptor binding studies and cell-based assays, confirmed that axitinib is a potent and selective inhibitor of VEGFRs 1, 2, and 3. Axitinib was shown to have antiangiogenic activity in a number of models including spontaneous pancreatic islet-cell tumors of RIP-TAG-2 transgenic mice model and demonstrated antitumor efficacy including marked cytoreductive antitumor activity, in multiple tumor models implanted in athymic mice.

The safety and efficacy of axitinib were evaluated in a randomized, open-label, multi-center Phase 3 study. Patients with advanced RCC (99% clear cell) whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized to receive axitinib (N=361) or sorafenib (N=362). There was a statistically significant advantage for axitinib over sorafenib for the primary PFS endpoint, 6.7 (95% CI: 6.3, 8.6) vs 4.7 (95% CI: 4.6, 5.6) months respectively ($p < 0.0001$). There was no statistically significant difference between the treatment arms in the secondary overall survival (OS) endpoint, 20.1 (95% CI: 16.7, 23.4) vs 19.2 (95% CI: 17.5, 22.3). The objective response rate (ORR) was 19.4% (95% CI: 15.4, 23.9) for axitinib and 9.4% (95% CI: 6.6, 12.9) for sorafenib. The most common (≥20%) adverse reactions observed in this study following treatment with axitinib were diarrhea (55%), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%), dysphonia (31%), palmar-plantar erythrodysesthesia (hand-foot) syndrome (27%), weight decreased (25%), vomiting (24%), asthenia (21%), and constipation (20%).[43]

Overall, the adverse events reported for axitinib in clinical studies are considered manageable, generally reversible and expected for this class of agents. For single-agent axitinib, the most common treatment-emergent all-causality AEs reported from 1474 cancer patients were: diarrhoea (55%), hypertension (51%), fatigue (47%), decreased appetite (40%), nausea (33%), weight decreased (32%), dysphonia (31%), palmar-plantar erythrodysaesthesia syndrome (29%), hypothyroidism and vomiting (23% each), constipation (20%), and proteinuria (20%).

Complete information for axitinib may be found in the SRSD, which for this study is the Investigator Brochure.[35] Further information may be found in the axitinib USPI.[36]

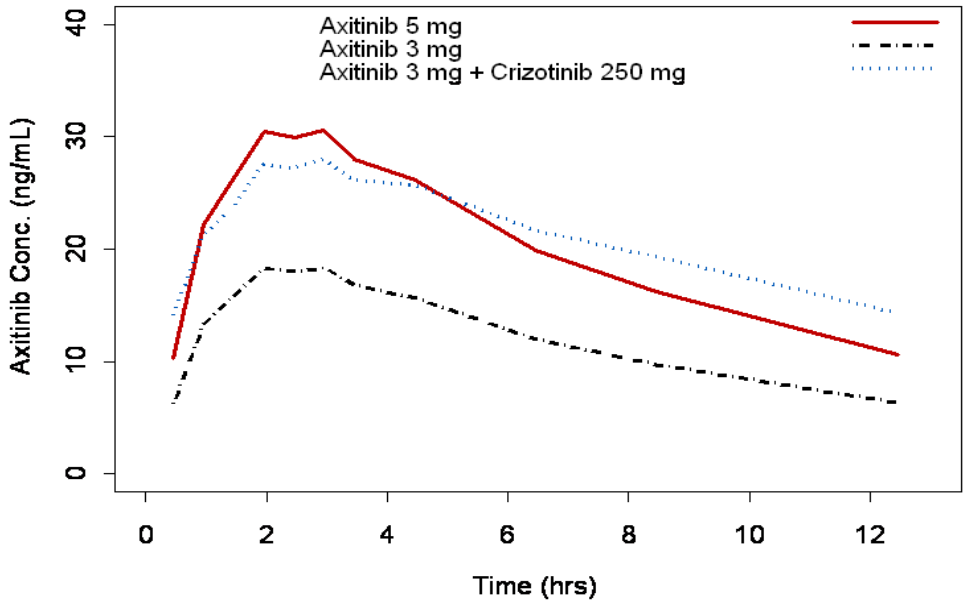
1.2.5. Rationale for Starting Doses of Axitinib and Crizotinib

Nonclinical and clinical pharmacokinetic (PK) data for crizotinib are reported in the crizotinib Investigator's Brochure.[29] In nonclinical studies pharmacokinetic/ pharmacodynamic (PK/PD) analyses for inhibition of c-MET/HGFR activity established a targeted efficacious concentration (C_{eff}) range of 40 to 62 ng/mL (8.1 to 12.8 nM, free drug). In clinical studies, repeated oral administration of crizotinib at 250 mg BID for 15 days or longer resulted in a median trough plasma concentration of 274 ng/mL (57 nM, free drug).

The RP2D and approved dose in ALK-positive patients is 250 mg BID.[29,34] Based on simulations, 250 mg every day (QD), 200 mg BID and 250 mg BID doses of crizotinib are expected to yield trough plasma concentrations exceeding crizotinib's Ceff for c-MET. In consideration of safety, the axitinib plus crizotinib combination will be first tested using a crizotinib starting dose of 200 mg BID (RP2D-1). The target crizotinib dose in the combination will be the currently approved dose of 250 mg BID. Dose de-escalation to crizotinib 250 mg QD will be allowed in the event of toxicity. Dose escalation and de-escalation will be based on DLTs.

The currently approved starting dose for axitinib is 5 mg PO BID.[35] Clinical PK data for crizotinib indicate that crizotinib is a moderate time-dependent cytochrome P450 (CYP) 3A4/5 inhibitor.[29] Axitinib is primarily metabolized by CYP3A4/5 as evidenced by a 2-fold increase in axitinib plasma exposures noted in the presence of the strong CYP3A4/5 inhibitor, ketoconazole.[35] Hence, there is a potential for increased axitinib exposure (by approximately 50%) in the presence of crizotinib. Considering this potential drug-drug interaction and the overlapping toxicities of axitinib and crizotinib (such as diarrhea, nausea, vomiting and fatigue), the starting dose of axitinib has been decreased to 3 mg PO BID for this study. Based on PK simulations, 3 mg PO BID axitinib in combination with crizotinib is predicted to provide similar plasma exposure to axitinib 5 mg PO BID alone (Figure 1). During the Dose Escalation Phase, the starting dose of axitinib may be increased to 5 mg BID or decreased to 2 mg BID in subsequent cohorts based on toxicity. Dose escalation and de-escalation will be based on DLTs. Axitinib is not expected to affect crizotinib exposure.

Figure 1. Pharmacokinetic Simulations Indicating the Predicted Increase in Exposure of Axitinib when Combined with Crizotinib



2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To assess the safety and tolerability of axitinib in combination with crizotinib in patients with solid tumors and advanced RCC in order to estimate the MTD (or MFD) and select the RP2D.

Secondary Objectives

- To evaluate the overall safety profile.
- To characterize the PK of axitinib and crizotinib when administered in combination and to assess the effect of crizotinib on the PK of axitinib (Dose Escalation Phase and at least 8 PK-evaluable subjects in Dose Expansion Phase Cohort 1 only).
- To characterize the effects of axitinib in combination with crizotinib on QTc.
- To document the anti-tumor activity of axitinib in combination with crizotinib in advanced RCC patients.
- To explore the pharmacodynamic effect of axitinib in combination with crizotinib in blood.
- To characterize the alterations and/or expression profiles of genes, proteins, and RNAs relevant to angiogenesis (eg, Ang-2), drug targets (eg, c-MET) and sensitivity and/or resistance (eg, PBRM1) to axitinib in combination with crizotinib in tumor and/or blood.

2.2. Endpoints

Primary Endpoint

- First-cycle DLTs.

Secondary Endpoints

- Adverse events as characterized by type, frequency, severity (as graded by NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.03), timing, seriousness and relationship to study therapy.
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v.4.03) and timing.
- Vital signs (blood pressure, pulse rate, weight, ECOG Performance Status [PS]).
- QTc interval.

- PK parameters of axitinib and crizotinib assuming steady state is achieved for both drugs: C_{max}, T_{max}, AUC_{0-12}, CL/F and V_z/F as data permit.

- Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

- Time-to-event endpoints (Dose Expansion Phase Cohorts only): Duration of Response (DR) and PFS.

- Pre- and post-dose blood levels of plasma and serum biomarkers.

- Baseline and at progression plasma, serum and tumor tissue biomarkers (eg, c-MET, HGF).

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of axitinib in combination with crizotinib in adult patients with advanced solid tumors.

This clinical study will be composed of two phases:

- Dose Escalation Phase: This phase will estimate the MTD in dose escalation cohorts in patients with advanced solid tumors. The modified toxicity probability interval (mTPI) method will be applied in the Dose Escalation.

- Dose Expansion Phase: This phase will confirm the safety and tolerability and explore the antitumor activity of axitinib in combination with crizotinib in two cohorts of patients with advanced RCC.

All patients will receive axitinib in combination with crizotinib in 28-day cycles.

To understand the PK effects of crizotinib on axitinib, a 7-day lead-in period of single-agent axitinib directly preceding the administration of the crizotinib and axitinib combination will be included prior to Cycle 1 in the Dose Escalation Phase of the study. Axitinib is not expected to affect crizotinib exposure so there will be no PK study with a lead-in period of single-agent crizotinib. The Dose Expansion Phase Cohort 1 will be used to further study crizotinib and axitinib pharmacokinetic interactions; in this cohort, the PK profile for axitinib single agent during the 7-day lead-in period will be compared to that of axitinib in combination with crizotinib during Cycle 1 (Figure 2). Patients participating in serial PK sampling (all patients in the Dose Escalation Phase and at least 8 evaluable patients in Cohort 1 of the Dose Expansion Phase) need to receive at least 3 consecutive days of axitinib treatment prior to axitinib PK sample collection (on Lead-in Day 7 and Cycle 1 Day 15). If, for any reason, this is not feasible, the patient will be replaced. No lead-in period will be included in the Dose Expansion Cohort 2 (Figure 3).

Figure 2. Study Schema – Dose Escalation Phase and Dose Expansion Phase Cohort 1 (selected patients for PK sample collection)

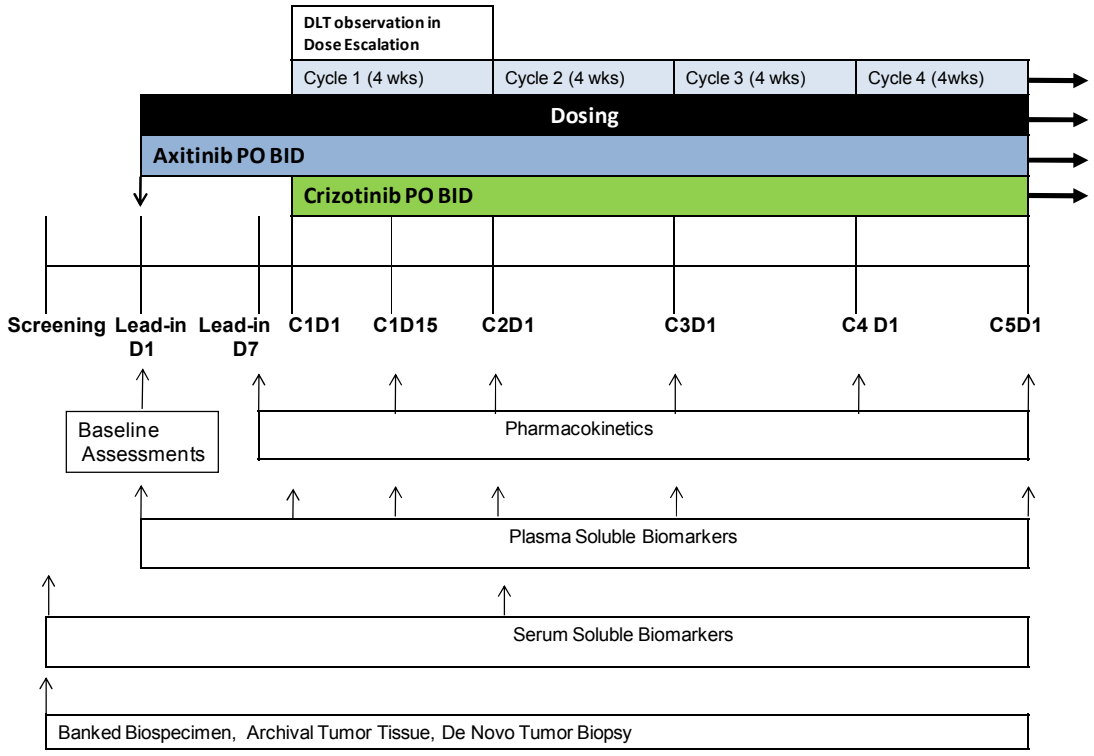
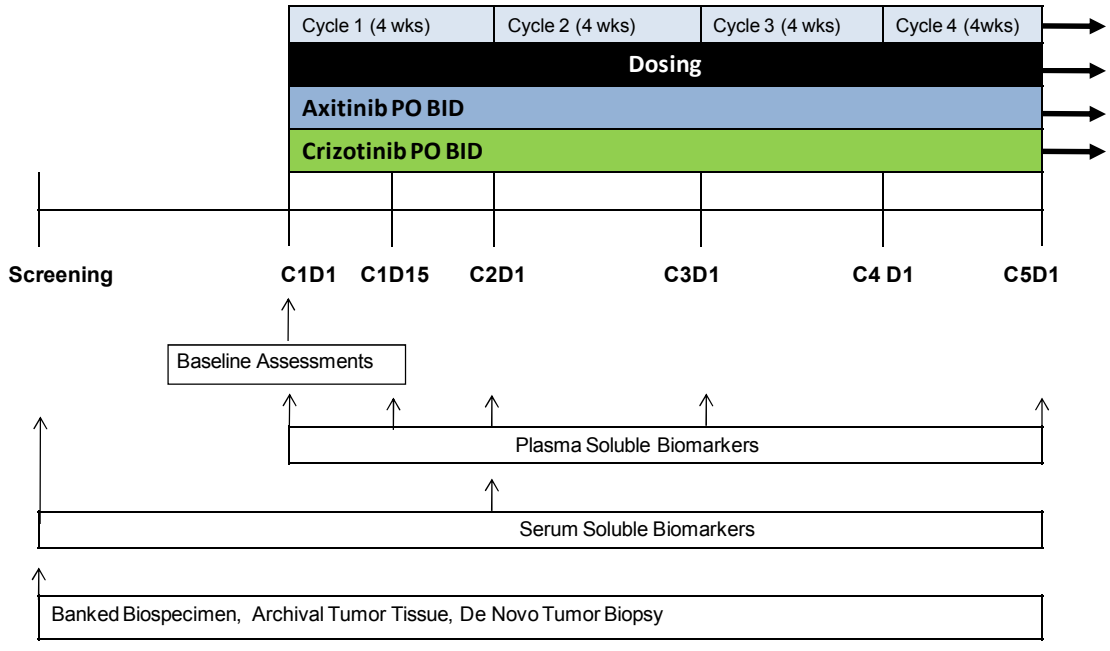


Figure 3. Study Schema – Dose Expansion Phase Cohort 1 (patients with no PK sample collection) and Dose Expansion Phase Cohort 2 (all patients)



In all patients, treatment with investigational product will continue until either disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the Sponsor. Patients with unacceptable toxicity attributed to one of the two investigational products may be eligible for continued treatment with the other investigational product (after discussion between the Investigator and the Sponsor). Patients with disease progression but who are still experiencing clinical benefit will be eligible for continued treatment with single agent axitinib or axitinib combined with crizotinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Anti-tumor activity will be evaluated every 8 weeks after Cycle 1 Day 1 using RECIST version 1.1. Given the safety profile of crizotinib, in addition to standard safety tests, ophthalmology examinations will be carried out to assess any vision changes. Based on the safety profile of axitinib, blood pressure will be monitored throughout the treatment period, as well as thyroid function.

ECG measurements will be taken throughout the treatment period in all patients and in conjunction with PK sampling in patients from the Dose Escalation Phase and the Dose Expansion Phase Cohort 1. Archived tumor tissues will be collected for all patients. De novo tumor biopsy will be collected for the patients in the Dose Expansion Phase Cohort 2. For all patients a second biopsy might be provided on a voluntary basis at the time of disease progression. Biomarker studies on tumor tissue and blood will be carried out to help understand the mechanism of action of the axitinib plus crizotinib combination, as well as potential mechanisms of resistance. Such results may help in the future development of this combination. These analyses may also result in the identification of potential biomarkers of response to the axitinib plus crizotinib combination, ultimately leading to development of a patient selection strategy for further clinical investigation. As such collection and analysis of the archival tumor tissue as well as de novo tumor biopsies at baseline and at time of progression will be paramount to generate such knowledge.

Up to 65 patients are expected to be enrolled in the study.

3.1.1. Dose Escalation Phase

3.1.1.1. Starting Doses for Axitinib and Crizotinib (Dose Level 1)

The rationale for the starting doses is given in Section 1.2.5. The starting doses (Dose Level 1) are axitinib 3 mg BID in combination with crizotinib 200 mg BID in 28-day cycles.

3.1.1.2. DLT Observation Period

Patients will be monitored for the occurrence of DLTs. For dose escalation purposes, the DLT observation period is Cycle 1 (28 days) (Figure 2).

Patients who discontinue treatment before completing the DLT observation period and who do not take at least 75% of the planned doses of both axitinib and crizotinib for reasons other than treatment related toxicity (for example, missed appointments, misplaced study drug supplies, development of rapidly progressing disease) will be replaced.

3.1.1.3. Criteria for Dose Escalation

Dose escalation and de-escalation will follow a matrix, "Up-and-Down" design, using doses of crizotinib and axitinib as shown in Table 1.

Table 1. Dose Levels in Dose Escalation Phase

Dose Level	Crizotinib	Axitinib
-1B	250 mg QD	3 mg BID
-1A	200 mg BID	2 mg BID
1 (Starting Dose Level)	200 mg BID	3 mg BID
2A	250 mg BID	3 mg BID
2B	200 mg BID	5 mg BID
3	250 mg BID	5 mg BID

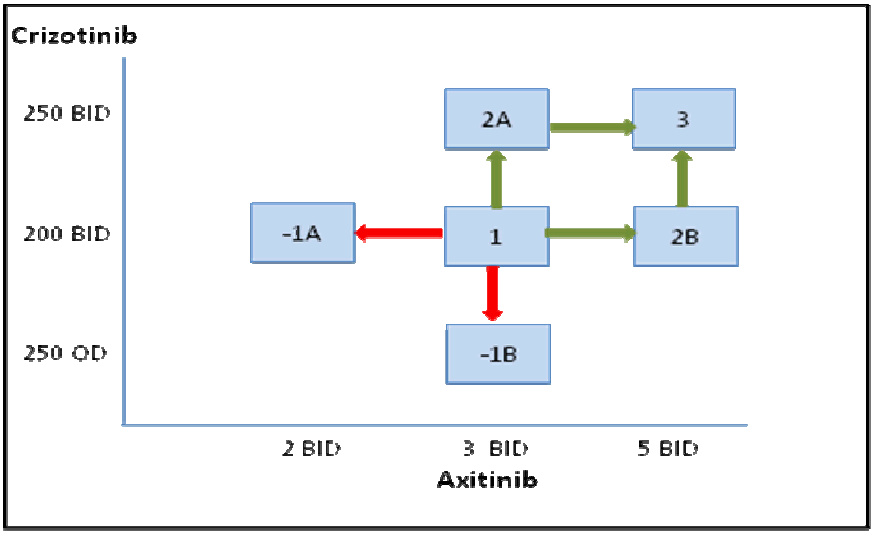
BID: twice daily; QD: once daily

The proposed doses, schedule(s) and PK timepoints may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data.

In this dosing algorithm there are up to 6 potential dose levels: (-1B) crizotinib 250 mg QD + axitinib 3 mg BID; (-1A) crizotinib 200 mg BID + axitinib 2 mg BID; (1) crizotinib 200 mg BID + axitinib 3 mg BID; (2A) crizotinib 250 mg BID + axitinib 3 mg BID; (2B) crizotinib 200 mg BID + axitinib 5 mg BID and (3) crizotinib 250 mg BID + axitinib 5 mg BID.

The matrix approach allows for parallel dose cohorts exploration as escalations and de-escalations are called for based upon toxicity results. Possible dose escalation/de-escalation scenarios based on the starting (1) dose level tolerability are illustrated in Figure 4.

Figure 4. Possible Scenarios for Dose Escalation/De-escalation Based on Dose Level Tolerability



The arrows represent either dose de-escalation (red arrow) or dose escalation (green arrows).

During the course of the study, only 1 investigational product (crizotinib or axitinib, but not both) can be dose escalated or de-escalated in the next cohort.

There are several potential dosing sequences for escalation or de-escalation of crizotinib + axitinib. 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. The sequences are mutually exclusive, meaning only one of the sequences will be followed through the course of the study. Some possible sequences are listed below in Table 2.

Table 2. Possible Dose-Finding Sequences

Dose 1 meets escalation criteria in the initially enrolled cohort	Dose 1 meets de-escalation criteria in the initially enrolled cohort
1 → (2A, 2B) → 3	1 → (-1A, -1B) → 1 → (2A, 2B) → 3
1 → (2A, 2B)	1 → (-1A, -1B) → 1 → (2A, 2B)
1 → (2A, 2B) → 3 → (2A, 2B)	1 → (-1A, -1B) → 1
1 → (2A, 2B) → 3 → (2A, 2B) → 1	1 → (-1A, -1B)
1 → (2A, 2B) → 3 → (2A, 2B) → 1→ (-1A, -1B)	

Dosing will begin at Dose Level 1 and escalated or de-escalated according to Table 1. The escalation/de-escalation rules will follow the mTPI method[38] (see Section 9.2 and Appendix 5). Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current cohorts at the same dose level to determine where future cohorts should involve dose escalation, no change in dose, or dose de-escalation. As an example, if the total number of patients (cumulative in the study from prior and current cohorts) treated at the current dose combination is 3 the following dosing rules are applied:

- 0 DLT → escalate;
- 1 DLTs → remain at the same dose;
- 2 DLTs → de-escalate;
- 3 DLTs → de-escalate and consider current dose as intolerable.

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

- The target enrollment cohort size is 3 patients. The first 3 patients treated in Dose Level 1 cohort will initiate dosing sequentially, at least 2 days apart to allow for the initial evaluation of toxicities and tolerability. If there are no safety concerns, any additional patients enrolled to this dose cohort will not be required to initiate dosing sequentially.
- The next cohort can be enrolled when all patients at the current dose cohort have been evaluated for 28 days of the first treatment cycle, or experience a dose limiting toxicity (DLT), whichever comes first.

- If a patient withdraws from the study before receiving at least 75% of the planned first-cycle dose of both axitinib and crizotinib for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.

- The dose-finding component of the trial is completed when at least 10 evaluable patients have been treated at the highest dose associated with DLT rate <0.33. It is estimated that approximately 25 DLT evaluable patients will need to be enrolled to reach 10 DLT-evaluable patients at the estimated MTD.

- The proposed doses, schedule, and PK timepoints may be reconsidered and amended during the study based on the emerging safety and pharmacokinetic data.

- The RP2D will be confirmed in the Dose Expansion Phase, taking into account the MTD/MFD determination from the Dose Escalation Phase, and other factors related to safety, efficacy, and PK/PD involving all available data from tests cohorts.

No intra-patient dose escalation will be permitted in the Dose Escalation Phase.

Once an MTD/MFD has been identified at the end of the Dose Escalation Phase, that dose level may be expanded with up to additional 10 patients patients to allow the collection of additional PK and/or safety data.

3.1.2. DLT Definition

Severity of adverse events will be graded according to NCI CTCAE version 4.03 (See Appendix 3). For the purpose of Dose Escalation, any of the following adverse events occurring during the DLT observation period (Cycle 1), that are attributable to one, the other, or both agents in the combination will be classified as DLTs:

- Hematologic:
  - Grade 4 neutropenia.
  - 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 one hour.
  - Grade ≥3 neutropenic infection.
  - Grade ≥3 thrombocytopenia with bleeding.
  - Grade 4 thrombocytopenia.

- Non-hematologic:
  - Grade ≥3 toxicities (except asymptomatic hypophosphatemia, hyperuricemia without signs and symptoms of gout, and tumor lysis syndrome).
  - Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy.
  - Grade 3 hypertension will be considered a DLT if the event is persistent despite use of anti-hypertensive medications.
- In an asymptomatic patient, Grade 3 QTc prolongation (QTc ≥501 msec) will first require immediate repeat testing, re-evaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTc prolongation persists, then the event should be considered a DLT.
- Failure to deliver at least 75% of dose of each investigational product due to toxicities attributable to one or both investigational products.

3.1.3. Maximum Tolerated Dose Definition

The MTD estimate is the highest dose of axitinib and crizotinib associated with the occurrence of DLTs in <33% of DLT-evaluable patients (see Section 9.1) .

3.1.4. Dose Expansion Phase Test Dose

The Expansion Test Dose will be either the MTD or the MFD, ie, the highest tested dose that is declared safe and tolerable by the Investigators and Sponsor.

3.1.5. Dose Expansion Phase

The Dose Expansion Phase will test axitinib in combination with crizotinib in patients with advanced RCC who are at their first diagnosis (Cohort 1) or have recurred during or after a VEGF-pathway inhibitor containing regimen (Cohort 2).

All patients in the Dose Expansion Phase may be enrolled simultaneously. A total of up to 20 patients will be enrolled into each Dose Expansion Phase Cohort. PK samples will be collected from at least 8 evaluable patients in Dose Expansion Phase Cohort 1.

Further experience in the Dose Expansion Phase Cohorts may result in the need to explore a lower Expansion Test Dose in one or both populations. Only doses declared safe in the Dose Escalation Phase will be considered.

For axitinib, intra-patient dose escalation to higher doses may be permitted in Cycle 2 and beyond (see Section 5.3.2.1).

3.2. Recommended Phase 2 Dose

The RP2D is the dose of axitinib and crizotinib in combination chosen for further study based on Phase 1 study results. If the MTD/MFD proves to be clinically feasible for long term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD/MFD may result in a RP2D dose lower than the MTD/MFD.

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:

    a. Dose Escalation Phase:

        - Histologically or cytologically confirmed diagnosis of advanced solid tumor that is resistant to standard therapy or for which no standard therapy is available.

        - Mandatory archival tumor tissue (formalin-fixed, paraffin-embedded [FFPE] tissue block(s) from either initial diagnosis or recurrence or metastatic site, or at least 12 unbaked, unstained slides). In cases where archival tumor tissue is not available, a de novo biopsy must be obtained for this purpose.

    b. Dose Expansion Phase:

        - Histologically or cytologically confirmed advanced RCC with a component of clear cell subtype, and:

            - Cohort 1: no prior systemic therapy directed at advanced RCC; or

            - Cohort 2: at least one but no more than two prior systemic treatment regimens directed at advanced RCC, with at least one prior therapy being a regimen containing an approved VEGF-pathway inhibitor, and resistance to the most recently received approved VEGF-pathway inhibitor. Resistance is defined as disease progression as per RECIST version 1.1 while on treatment with a VEGF-pathway inhibitor.

- Mandatory tumor tissue/biopsy collection:
  - Cohort 1 and Cohort 2: mandatory archival tumor tissue (FFPE tissue block(s) from initial diagnosis or at least 12 unbaked, unstained slides). In cases where archival tumor tissue is not available, a de novo biopsy must be obtained for this purpose.
  - Cohort 2 only: baseline de novo tumor biopsy collection. Alternatively, a recently obtained FFPE tumor tissue block from a resection or biopsy of a primary, recurrent or metastatic lesion can be provided if the following criteria are met: 1) the biopsy or resection was performed within 4 months of patient registration AND 2) the patient has not received any new intervening systemic anti-cancer treatment from the time the tissue was obtained and the patient registration.
- At least one measureable lesion as defined by RECIST version 1.1.

2. Age ≥18 years.
3. ECOG Performance Status 0 or 1 (see Appendix 1).
4. 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.
5. Adequate renal function, including:
   a. Serum creatinine ≤1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution and;
   b. Urinary protein <2+ by urine dipstick. If dipstick is ≥2+, then a 24-hour urinary protein <2 g per 24 hours.
6. Adequate liver function, including:
   a. Total serum bilirubin ≤1.5 x ULN;
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN (≤5.0 x ULN if there is tumor involvement in the liver);
   c. Alkaline phosphatase ≤2.5 x ULN; (≤5 x ULN in case of bone metastasis).

7. INR or prothrombin time (PT) <1.5 x ULN.

8. If applicable, end of prior anticancer systemic treatment ≥2 weeks (≥4 weeks for bevacizumab + IFN) of patient registration, with resolution of all treatment-related toxicity to baseline severity or Grade ≤1 except for alopecia, hypothyroidism and other AEs not constituting a safety risk by Investigator judgment.

9. No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings taken at least 1 hour apart. The baseline systolic BP readings must be ≤150 mm Hg, and the baseline diastolic BP readings must be ≤90 mm Hg.

10. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

11. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

12. Serum/urine pregnancy test (for females of childbearing potential) negative at screening and at the baseline visit (before the patient may receive the investigational product).

13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 90 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the Investigator, he/she is biologically capable of having children and is sexually active.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Prior therapy with an agent that is known or proposed to be active by action on c-MET/HGF including but not limited to cabozantinib (XL184), foretinib (XL880), onartuzumab (MetMAb) and rilotumumab (AMG102).

2. Major surgery <4 weeks or radiation therapy <2 weeks of patient registration. Prior palliative radiotherapy (≤10 fractions) to metastatic lesion(s) is permitted, provided it has been completed 48 hours prior to the initiation of study medication and there is at least one measurable lesion that has not been irradiated (except patients in Dose Escalation Phase, who are not required to have any measurable lesion).

3. 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 hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
- Malabsorption syndromes.

4. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.

5. Evidence of inadequate wound healing, active bleeding disorder or other history of significant bleeding episodes within 30 days before study entry.

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

7. History of or known active seizure disorder, brain metastases, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease.

8. Any of the following within the 12 months prior to investigational product administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, or machine-read ECG with QTc interval ≥481 msec.

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

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

11. Use of drugs or foods that are known strong CYP3A4/5 inhibitors within 7 days prior to the first dose of investigational product including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

12. Use of drugs that are known strong CYP3A4/5 or CYP1A2 inducers within 12 days prior to the first dose of investigational product, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

13. Use of drugs that are CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (* withdrawn from U.S. market).

14. Dose Expansion Phase only: diagnosis of any other malignancy within 2 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix.

15. Patients who are investigational site staff members directly involved in the conduct of the trial 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 trial.

16. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

17. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or end-stage renal disease on 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.

18. 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 two highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days after last dose of investigational product.

4.3. Life Style Guidelines

4.3.1. Sunlight Exposure

Patients will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the patients' exposure to light including high intensity ultraviolet B light (UVB) sources such as tanning beds, tanning booths and sunlamps. Patients should be encouraged to apply sunscreen/sunblock daily.

4.3.2. Contraception

In this study, male patients who are able to father children and female patients who are of childbearing potential will receive axitinib, which has been associated with teratogenic risk,

in combination with crizotinib. Those who, in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use two (2) methods of highly effective contraception throughout the study and continue to do so 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 chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception method 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:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are 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, suppository).

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.

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

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- 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 having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects 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.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk 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 patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used 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 study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they 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).

5.1. Allocation to Treatment

Dose level allocation will be performed by the Sponsor after patients have given their written informed consent and have completed the necessary baseline assessments.

The site staff will fax or e-mail a complete Registration Form to the designated Sponsor study team member(s) requesting approval for patient enrollment.

After review of patient's eligibility and concomitant medications, the Sponsor will approve patient's enrollment, if appropriate, and assign a patient identification number, which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient.

The Sponsor will fax or email the approved Registration Form reporting the patient identification number to the site.

No patient shall receive investigational product until the Investigator or designee has received the following information in writing from the Sponsor:

- Confirmation of the patient's enrollment.
- Specification of the dose level for that patient.
- Permission to proceed with dosing the patient.

The Sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date.

5.2. Investigational Product Supplies

Axitinib (AG-013736) and crizotinib (PF-02341066) will be supplied for the study by the Global Clinical Supply, Worldwide Research and Developement. Drug supplies will be shipped to the study sites with a Drug Shipment & Proof of Receipt form. This form should be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment & Proof of Receipt form.

5.2.1. Dosage Form(s) and Packaging

5.2.1.1. Axitinib

Axitinib will be supplied for oral administration as 1 mg and 5 mg film-coated tablets in High Density Polyethylene (HDPE) bottles with desiccant.

5.2.1.2. Crizotinib

Crizotinib will be supplied for oral administration as capsules containing 200 mg, or 250 mg of study medication and will be packaged in HDPE bottles.

5.2.2. 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 chemotherapeutic agents.

Axitinib will be dispensed in opaque plastic bottles to protect the compounds from light. Axitinib is a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the American Society of Hospital Pharmacists (ASHP), Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, American Hospital Formulary Service (AHFS) Drug Information (1999) and its references. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

Axitinib and crizotinib will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. In the event of dose modification, a request should be made of the patient to return all previously dispensed medication to the clinic.

5.3. Administration

Axitinib and crizotinib will be each administered orally BID at approximately the same time in the morning and evening on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity (see Section 5.3.2.2). The two drugs can be taken together and the evening dose of each drug should be taken approximately 12 hours after the morning dose. Both drugs may be administered without regard to meals. Cycles are defined in 28-day periods to facilitate scheduling of visits and assessments. Capsules must not be opened or dissolved.

A dosing card will be provided to the patients to provide guidance for the correct use of the two drugs.

Patients must be instructed that if they miss a dose or vomit anytime after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late up to 3 hours for axitinib dose or up to 6 hours for crizotinib dose before the next scheduled dose, otherwise, it should be skipped and dosing resumed with subsequent doses as prescribed. Patient must be instructed to record all doses (and missed or vomited doses) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose.

5.3.1. Food Requirements

Both axitinib and crizotinib can be taken with or without food. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of axitinib and crizotinib.

5.3.2. Recommended Dose Modifications

Axitinib and crizotinib dose levels for intra-patient dose modification are listed in Table 3 and Table 4, respectively.

Table 3. Axitinib Dose Levels

Dose
10 mg BID
7 mg BID
5 mg BID
3 mg BID
2 mg BID

Table 4. Crizotinib Dose Levels

Dose
250 mg BID
200 mg BID
250 mg QD

Intra-patient dose escalation is permitted in the Dose Expansion Phase only and for axitinib only.

5.3.2.1. Axitinib Intra-Patient Dose Escalation

Patients enrolled to either Dose Expansion Phase Cohort, who are in Cycle 2 or beyond, and who tolerate axitinib with no drug-related grade ≥3 adverse events for 2 consecutive weeks have the option to have their axitinib dose increased by one dose level in subsequent cycles as indicated in Table 3, up to a maximum dose of 10 mg BID (unless the patient's BP is >150/90 mm Hg or the patient is receiving antihypertensive medication). Since crizotinib may cause inhibition of axitinib metabolism, particular attention should be provided to a patient's overall safety profile prior to implementing intra-patient dose escalation for axitinib. The Sponsor must be notified of the decision to increase the dose of axitinib.

5.3.2.2. Dose Modifications in Case of Drug-Related Toxicity

Every effort should be made to administer investigational product on the planned dose and schedule.

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 Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in two ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle.
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Patients will be monitored closely for toxicity, and axitinib and/or crizotinib treatment may be adjusted by dosing interruption with or without dose reduction as indicated below. Dose modification can occur independently for the 2 drugs. Dosing interruption and/or intrapatient dose reduction by 1, and if needed, 2 doses will be allowed depending on the type and severity of toxicity encountered. If the patient is already at the lowest dose for one or the other study drug, the relevant study drug should be permanently discontinued. Management of patients requiring more than 2 dose reductions should be discussed with the Sponsor.

Dose modifications for toxicity can occur in both the Dose Escalation and Dose Expansion Phases. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Toxicities should initially be attributed to either axitinib or crizotinib and managed accordingly.

Dosing CRFs should be utilized to document each time study medication is modified, started and stopped.

Recommended dose modifications in case of drug-related toxicity are shown in Table 5.

Table 5. Dose Modifications for Drug-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Hematologic Laboratory Investigations	Grade 1 or Grade 2	**Axitinib:** Continue at the same dose level.
		Crizotinib: Continue at the same dose level.
	Grade 3	**Axitinib**: Continue at the same dose level.
		Crizotinib: Withhold until recovery to Grade ≤2. Then, resume at the same dose level or reduce by 1 dose level as per Investigator judgement. Grade 3 lymphopenia not associated with clinical events, eg, opportunistic infection: study treatment may continue without interruption.
	Grade 4	**Axitinib:** Withhold until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment. Grade 4 lymphopenia not associated with clinical events, eg, opportunistic infection: study treatment may continue without interruption.
		Crizotinib: Withhold until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment as per Investigator judgement or after discussion with the Sponsor. Grade 4 lymphopenia not associated with clinical events, eg, opportunistic infection: study treatment may continue without interruption.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Non-hematologic Toxicites and/or Laboratory Abnormalities (excluding exceptions mentioned below)	Grade 1 or Grade 2	**Axitinib:** Continue at the same dose level.
		Crizotinib: Continue at the same dose level.
	Grade 3	**Axitinib:** Reduce by 1 dose level. Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry laboratory abnormalities: continue at the same dose level as per Investigator judgement.
		Crizotinib: Withhold until recovery to Grade ≤1, or to baseline Grade. Then, resume at the same dose level or reduce by 1 dose level as per Investigator judgement. Grade 3 hypophosphatemia and/or hyperuricemia without clinical symptoms: study treatment may continue without interruption as per Investigator judgement. Persistent Grade 3 nausea, vomiting or diarrhea despite maximal medical therapy: reduce by 1 dose level.
	Grade 4	**Axitinib:** Withhold current dose until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment. Grade 4 asymptomatic biochemistry laboratory abnormality: study treatment may continue without interruption.
		Crizotinib: Withhold current dose until recovery to Grade ≤1, or to baseline Grade. Then, reduce by 1 dose level and resume treatment, or permanently discontinue as per Investigator judgement. Grade 4 hypophosphatemia and/or hyperuricemia without clinical symptoms: study treatment may continue without interruption as per Investigator judgement. Persistent Grade 4 vomiting or diarrhea despite maximal medical therapy: reduce by 1 dose level.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Laboratory Investigations: ALT increase with total bilirubin <2 X ULN (in absence of cholestasis or hemolysis)	Grade 1	**Axitinib**: Continue at the same dose level.
		Crizotinib: Continue at the same dose level.
	Grade 2	**Axitinib**: Continue at the same dose level.
		Crizotinib: Continue at the same dose level. Obtain repeat ALT and total bilirubin when symptomatic or within 7 days.
	Grade 3	**Axitinib:** Reduce by 1 dose level.
		Crizotinib: Withhold until recovery to Grade ≤1, or to baseline Grade. Then, reduce by 1 dose level and resume treatment. If Grade 3 ALT elevation recurs, then reduce further (at most by 2 dose levels from the initial dose level). If recurrence at dose level -2, then discuss with Sponsor whether or not to discontinue permanently. If ALT elevation does not recur after at least 4 weeks, then the dose may be escalated by single dose-level increments up to the initial dose level.
	Grade 4	**Axitinib:** Withhold current dose until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment.
		Crizotinib: Withhold until recovery to Grade ≤1, or to baseline Grade. Then, reduce by 1 dose level and resume treatment. If Grade 4 ALT elevation recurs, then reduce further (at most by 2 dose levels from the initial dose level). If recurrence at dose level -2, then discuss with Sponsor whether or not to discontinue permanently. If ALT elevation does not recur after at least 4 weeks, then the dose may be escalated by single dose-level increments up to the initial dose level.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Laboratory Investigations: ALT increase and bilirubin increase ≥2 X ULN (in absence of cholestasis or hemolysis)	Grade 1	**Axitinib**: Continue at same dose level.
		Crizotinib: Continue at the same dose level. Obtain repeat ALT and total bilirubin within 48 hours.
	Grade 2	**Axitinib:** Continue at the same dose level.
		Crizotinib: Permanently discontinue.
	Grade 3	**Axitinib:** Reduce by 1 dose level.
		Crizotinib: Permanently discontinue.
	Grade 4	**Axitinib:** Withhold current dose until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment.
		Crizotinib: Permanently discontinue.
Pneumonitis (not attributable to disease progression, infection, other pulmonary disease, or radiation effect. To confirm diagnosis see Section 5.3.3.1)	Any Grade	**Axitinib:** Continue at same dose level *
		Crizotinib: Permanently discontinue.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Electrocardiogram QT prolongation	Grade 1	**Axitinib:** Continue at the same dose level*
		Crizotinib: Continue at the same dose level
	Grade 2	**Axitinib**: Continue at the same dose level* Assess and correct electrolytes (particularly Ca+, K+, and Mg+) and concomitant medications.
		Crizotinib: Continue at the same dose level. Assess and correct electrolytes (particularly Ca+, K+, and Mg+) and concomitant medications.
	Grade 3	**Axitinib:** Reduce by 1 dose level.* Assess and correct electrolytes (particularly Ca+, K+, Mg+) and concomitant medications.
		Crizotinib: Withhold until recovery to Grade ≤1. Assess and correct electrolytes (particularly Ca+, K+, Mg+) and concomitant medications. Then, reduce by 1 dose level and resume treatment if no other cause for QTc prolongation is found, otherwise resume at the same dose level.
	Grade 4	**Axitinib:** Withhold current dose until recovery to Grade ≤2.* Then, reduce by 1 dose level and resume treatment.
		Crizotinib: Permanently discontinue.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
Bradycardia	Grade 1	**Axitinib:** Continue at the same dose level.*
		Crizotinib: Continue at the same dose level.
	Grade 2 or Grade 3	**Axitinib:** Continue at the same dose level.*
		Crizotinib: Withhold until recovery to Grade ≤1. 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 treatment at previous dose. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, then reduce by 1 dose level and resume treatment.
	Grade 4	**Axitinib:** Continue at the same dose level.*
		Crizotinib: Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted: withhold until recovery to Grade ≤1, then reduce to 250 mg QD and resume treatment, with frequent monitoring. Permanently discontinue for recurrence.
Vision Disorder	Grade 1 or Grade 2	**Axitinib:** Continue at the same dose level.*
		Crizotinib: Continue at the same dose level. ‡
	Grade 3	**Axitinib**: Continue at the same dose level.* If due to a thrombotic event, reduce by 1 dose level.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
		Crizotinib: Withhold until recovery to Grade ≤1. ‡ Then, reduce by 1 dose level and resume treatment.
	Grade 4	**Axitinib**: Continue at the same dose level.* If due to a thrombotic event, withhold current dose until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment.
		Crizotinib: Permanently discontinue. ‡
	‡ Repeat ophthalmologic consultation. For details see Section 7.1.6.	
Proteinuria	Dipstick negative or shows 1+ (Grade 1)	**Axitinib:** Continue at the same dose level.
		Crizotinib: Continue at the same dose level. §
	If dipstick shows >1+, perform 24 hour urine collection. Dosing may continue while waiting for test results	
	<2 g proteinuria/24 hour	**Axitinib:** Continue at the same dose level.
		Crizotinib: Continue at the same dose level. §
	≥2 g proteinuria/24 hours	**Axitinib:** Withhold until proteinuria is <2 g/24 hours. Repeat 24 hour urine collection for proteinuria and creatinine clearance (interval at Investigator discretion) until proteinuria is <2 g/24 hours. Then, resume at the same dose level or reduce by 1 dose level as per Investigator judgement.
		Crizotinib: Continue at the same dose level. §
Hypertension	2 systolic BP readings separated by at least 1 hour show systolic pressure	**Axitinib:** Continue at the same dose level See Section 5.3.2.3 for monitoring/management of axitinib-related hypertension

Toxicity	NCI CTCAE Severity Grade	Dose modifications
	≤150 mm Hg (one or both readings) And 2 diastolic BP readings separated by at least 1 hour show diastolic pressure ≤100 mm Hg (one or both readings)	**Crizotinib**: Continue at the same dose level. §
	2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	**Axitinib**: If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and continue at the same dose level. If on maximal antihypertensive treatment, reduce by 1 dose level. See Section 5.3.2.3 for monitoring/management of axitinib-related hypertension.
		Crizotinib: Continue at the same dose level. §
	2 systolic BP readings separated by at least 1 hour show systolic pressure >160 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	**Axitinib:** Withhold until BP is less than 150/100 mm Hg [1] and adjust antihypertensive medication. Then, reduce by 1 dose level and resume treatment. [1] If axitinib dosing is temporarily discontinued, patients receiving antihypertensive medications should monitor closely for hypotension. The plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption. See Section 5.3.2.3 for monitoring/management of axitinib-related hypertension
		Crizotinib: Continue at same dose level. §
	Recurrent hypertension following previous dose reduction (2 systolic BP readings separated by at least 1 hour show	**Axitinib:** Repeat dose reduction by one lower dose level. See Section 5.3.2.3 for monitoring/management of axitinib-related hypertension.

Toxicity	NCI CTCAE Severity Grade	Dose modifications
	systolic pressure >150 mm Hg) OR Recurrent diastolic BP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	**Crizotinib**: Continue at same dose level §

* Toxicity not reported in the Investigator Brochure of axitinib, Warning and Precautions section [35]
§ Toxicity not reported in the Investigator Brochure of crizotinib, Adverse Drug Reaction section [29]

5.3.2.3. Management of Axitinib-Related Hypertension

Patients will be issued BP cuffs (provided by the Sponsor) for home monitoring and instructed to measure their BP twice daily, prior to taking each dose. All BP measurements will be recorded in a diary and brought to the nurse or study coordinator at each clinic visit. Patients should contact the site for guidance if their systolic BP rises above 150 mm Hg, diastolic BP rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).

To treat an increase in BP, standard antihypertensives can be used (for example, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and dihydropyridine (DHP) calcium channel blockers) although bradycardic agents (such as beta adrenergic blockers with or without alpha-blocking properties, and non-DHP calcium channel blockers, clonidine, digoxin) should be avoided to the extent possible.[37]

5.3.3. Crizotinib-Related Adverse Events Safety Monitoring

5.3.3.1. Pneumonitis

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, then the following evaluations/procedures should be considered to confirm or exclude the diagnosis of pneumonitis during this period in the absence of disease progression, other pulmonary disease, infection, or radiation effects:

- Sputum gram stain and culture (induced sputum if needed) for bacterial, viral, fungal, protozoal, and mycobacterial pathogens.
- Blood culture should be performed in febrile patients. Consider appropriate serologies (mycoplasma, legionella, cytomegalovirus, other viruses, etc.).
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology).
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate - the BAL fluid should be sent for culture, microbiology, and cytology.
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- Plasma sample for BNP (B-type Natriuretic Peptide) to evaluate for evidence of congestive heart failure (CHF).

If clinically appropriate, high-dose corticosteroid treatment should be initiated. Should the event be fatal, an autopsy is highly recommended to confirm or exclude the diagnosis. See Table 5 for appropriate dose modifications.

5.3.3.2. Renal Cyst

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 usually developed from 2 to 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 and as scheduled per protocol. Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

5.3.4. Overdose Instructions

In the event of an overdose, the Sponsor should be contacted to discuss the details of the overdose and formulate a clinical management plan.

No information regarding overdose of crizotinib in humans is available. In Phase 3 study with axitinib for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1). In a clinical dose finding study with axitinib, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

No antidote exists for the treatment of crizotinib or axitinib overdose. In the event of an accidental overdose, the patient should be monitored for possible signs of toxicity as mentioned above, and general supportive care should be provided.

5.3.5. Compliance

An Investigational Product (IP) manual will be provided to the sites and will contain information about the drug supplies. A patient diary will be provided to the patients to aid in drug compliance. The diary will be maintained by the patient to include missed or changed doses.

Patients will be required to return all bottles of study medication at the beginning of each cycle. The number of tablets or capsules remaining will be documented and recorded at each clinic visit. The patient diary may also be used to support this part of the drug accountability process.

The site is to follow up (for example, via a telephone call) with each patient at Cycle 1 Day 3 (+ 3 days) to confirm that the patient understands and is in compliance with dosing instructions. The follow-up for dosing compliance by telephone is recommended also whenever there is a dose change.

5.4. 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.

- Crizotinib and axitinib should be stored at controlled room temperature (between 15-30°C) in provided packaging.

Storage conditions stated in the SRSD (ie, Investigator Brochure) will be superseded by the label storage.

All study drug supplies must be kept in a locked, limited access room. The study drug must not be used outside the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor. The Investigator and or site staff must report any unacceptable condition of the investigational product to the site monitor.

Investigators and site staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities.

The prescribed dose should be recorded in the patient's medical records. Drug dispensing needs to be verified and documented by a second individual and the forms must be signed by both the individual who dispensed the drug and the second individual who verified the dispensing. Copies must be provided to Pfizer.

All bottles of study drug must be returned to the Investigator by the patient. At the end of the trial, or at appropriate points during the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial 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. Destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

5.5. Concomitant Medication(s)

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 28 days post 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 axitinib and crizotinib is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed. Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance of selected adverse event provided in this protocol.

5.5.1. Inhibitors and Inducers of CYP Enzymes

The metabolism of crizotinib is predominantly mediated by the CYP3A4/5 isozymes in human liver microsomes and hepatocytes. Similarly, in vitro studies with human liver microsomes and recombinant CYP enzymes indicate that axitinib metabolism is primarily mediated by the drug-metabolizing enzyme CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1. Co-administration with drugs that are strong CYP3A4/5 inhibitors and inducers may change the plasma concentrations of crizotinib and axitinib.

The concurrent use of strong CYP3A4/5 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice, are not allowed in the study. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.

The concurrent use of strong CYP3A4/5 or CYP1A2 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in this study.

Crizotinib showed time-dependent inhibition of CYP3A4/5 isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9-fold) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A4/5. Caution must be exercised in patients receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A4/5, such as alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. In particular, co-administration of crizotinib with CYP3A4/5 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. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In vitro studies indicated that axitinib does not inhibit CYP3A4/5, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or UGT1A1 at therapeutic plasma concentrations.

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

5.5.2. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first cycle of treatment but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[41]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician 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 treating physician.

5.5.3. Anti Diarrhea, Anti Emetic Therapy

Patients may receive prophylaxis of treatment-induced diarrhea. Symptomatic care such as loperamide (Imodium®) is recommended (4 mg at first onset, then 2 mg every 2-4 hours until symptom-free for 12 hours, for diarrhea Grade ≥2). Other anti-diarrheal medications can be used per local standard of care.

Standard anti-emetics may be used for the treatment of nausea and/or vomiting. Taking the medication with food may reduce nausea. The use of anti-emetics for profilaxis may be considered.

5.5.4. Other Concomitant Medications

- Palliative and supportive care for disease-related symptoms, including pain medications, will be allowed to all patients on this trial.
- Patients with fever or infection requiring treatment should be treated with antimicrobials that are not prohibited due to their action on CYP enzymes as noted above.
- Packed red blood cell and platelet transfusions should be administered as clinically indicated.
- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/ paracetamol to a MAXIMUM total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.
- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, the administration of coumadin, other coumarin derivatives, or other anticoagulants may be allowed; appropriate monitoring of prothrombin time/International normalized ratio (PT/INR) should be performed.
- Patients on this trial may be supported with appropriate hormone replacement therapy as clinically indicated.

- Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

- The 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. It is important to counsel patients about the risk of bradycardia and inform them of what symptoms and signs to be aware of and actions to take.

- Crizotinib should be used with caution when administered concomitantly with medicinal products that are known to prolong QT interval and/or antiarrhythmics, or when it is administered to patients who have a history of or predisposition for QTc prolongation. When using crizotinib in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered.

5.5.5. Concomitant Surgery

No formal studies of the effect of axitinib on wound healing have been conducted, however caution is advised based on the mechanism of action. If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with axitinib must be interrupted at least 24 hours before the procedure and the patient BP should be monitored closely for hypotension. Patients may resume axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

The effect of crizotinib on wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect). In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

5.5.6. 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. Crizotinib treatment should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after.

If palliative radiotherapy is needed to control bone pain the sites of bone disease should be present at baseline.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see Schedule of Activities (SOA) and Assessments section (Section 7).

6.1.1. Archival Tumor Tissue

All patients will provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen, or, if not available, a de novo tumor biopsy must be obtained for this purpose in accordance with local institutional practice for tumor biopsies. For patients in the Dose Escalation Phase, the archival tumor tissue can be from either initial diagnosis or recurrence or metastatic site. For patients in the Dose Expansion the archival tumor tissue must be from the initial diagnosis. Formalin fixed, paraffin embedded (FFPE) tissue block of archival tumor tissue that contains sufficient tissue to generate at least 12 unstained slides, each with tissue sections that are 5 microns thick, will be collected. If no FFPE block is available, then at least 12 unbaked and unstained slides containing FFPE tissue sections, that are 5 microns thick must be provided.

6.1.2. De Novo Tumor Biopsy

A de novo tumor biopsy is mandatory for all patients enrolled in Dose Expansion Phase Cohort 2 and should be collected for this purpose in accordance with local institutional practice for tumor biopsies. This de novo biopsy must be taken no more than 28 days prior to registration. Alternatively, a recently obtained FFPE tumor tissue block from a resection or biopsy of a primary, recurrent or metastatic lesion can be provided if the following criteria are met: 1) the biopsy or resection was performed within 4 months of study start AND 2) the patient has not received any new intervening systemic anti-cancer treatment from the time the tissue was obtained and the study start.

Patients enrolled into the Dose Escalation Phase or into the Dose Expansion Phase Cohort 1 may provide a de novo biopsy on a voluntary basis. For those patients, this sample will be provided in addition to the archived tumor tissue that is required for enrollment, unless archived tumor tissue is not available in which case the de novo biopsy is mandatory.

In addition, a de novo tumor biopsy is encouraged at the time of progression from all patients.

The de novo biopsy will consist of an incisional or excisional biopsy, or a core needle biopsy, of a primary or metastatic lesion. Fine needle aspiration biopsies are not acceptable. The tumor tissue will be processed as specified in the Laboratory Manual.

6.2. Study Period

For treatment period procedures, see Schedule of Activities (SOA) and Assessments section (Section 7).

6.3. Follow-up Visit

For follow-up procedures see Schedule of Activities (SOA) and Assessments section (Section 7).

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 discontinuation of study treatment may include:

- Objective disease progression according to RECIST version 1.1; however, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single agent axitinib or axitinib plus crizotinib provided that the treating physician has determined that the benefit/risk for doing so is favorable;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study drugs, the Investigator (in discussion with the Sponsor) can continue the study treatment with the other study drug;
- Pregnancy;
- Significant protocol violation (post study start; includes patient noncompliance);
- 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;
- Refusal for further follow-up for survival;
- 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 the patient to return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study due to unacceptable toxicity or refusal of further treatment, the patient should undergo regular tumor assessments until disease progression or start of a new anticancer treatment or up to 18 months from last patient enrolled, whatever occurs first. If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further 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.

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 which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team 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, ECG (12-lead), laboratory assessments, including pregnancy tests and verification of concurrent medications.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two 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. Pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of studytreatment and additionally whenever one 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 administration of investigational product but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Board/Independent Ethics Committees (IRB/IECs) 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 CAE] version 4.03), timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessment

Haematology and blood chemistry will be drawn at the time points described in the Schedule of activities (SOA) and analyzed at local laboratories. The required laboratory tests are listed in Table 6.

Table 6. Required Laboratory Tests

Hematology	Chemistry	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT	Protein, glucose and blood. Urine dipstick for urine protein: If positive collect 24-hour and microscopic (Reflex Testing) Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	PT	For female patients of childbearing potential, serum or urine
Platelets	AST		INR	
WBC	Alk Phos			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium			
Absolute Eosinophils	Chloride			
Absolute Basophils	Calcium			
	Total Bilirubin***			
	BUN or Urea			
	Creatinine			
	Uric Acid			
	Glucose (non-fasted)			
	Albumin			
	Total Protein			
	Phosphorus or Phosphate			
	Thyroid Function Tests: TSH, free T3, free T4 (as indicated)			

*** For 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.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam to include weight, blood pressure, pulse rate, assessment of ECOG performance status and height; height will be measured at screening only. 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. Two blood pressure readings will be taken at least 1 hour apart at each clinic visit.

7.1.5. ECG Measurements

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Triplicate ECG measurements will be obtained at all time points except for a single ECG measurement at screening. For triplicate measures, three consecutive 12-lead ECGS will be collected approximately 2 minutes apart. It is required that the machine used has a capacity to calculate the standard intervals automatically. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. Additional ECGs will be performed as clinically indicated. If the QTc is prolonged (≥501 msec), then the ECG should be read by a cardiologist at the site for confirmation. Any manual overread done at site must be entered into the CRF as an unplanned ECG result. In case of a QTc interval measurement ≥501 msec (Grade ≥3) dosing should be interrupted, and permanently discontinued for a Grade 4 QTc prolongation. For Grade 3 or 4 QTc prolongations continuous ECG monitoring will be done under physician supervision until the QTc recovers to Grade ≤1. Triplicate ECG surveillance will again be performed when crizotinib is restarted on a reduced dose due to Grade 3 QTc prolongation. The timing of the triplicate assessment of ECGs should be prior to (0 hour) and 2-6 hours after morning dosing of crizotinib on Day 1 of Cycles 1, 2, and 3, and on Day 15 of Cycle 1. Additional ECGs will be performed as clinically indicated.

7.1.6. Ophthalmology Examinations

Ophthalmologic examinations for both right and left eyes will be performed at screening and should be performed by an ophthalmologist.

Ophthalmologic examinations should be repeated during the course of the study whenever a vision disorder AE is observed or CTCAE grade change occurs from a previous visit.

Best Corrected Visual Acuity and Refraction

Best corrected visual acuity will be assessed using a standard wall or projection chart (Snellen) before implementing any procedures that can affect vision (eg, pupil dilation). The same chart will be used throughout the study for a specific patient, and the right eye should be tested first. The refractive error also will be determined. The examiner should ensure that patients are seated comfortably and that they do not move their head forward or backward during testing. Patients will be told that the chart contains only letters.

The line read with 2 or fewer errors will be recorded. If 3 of the 5 letters on a line are read correctly, then the patient will be given credit for that line. For example, if the patient reads 20/25 +3, then 20/20 will be recorded.

A decrease in best-corrected visual acuity of 3 lines or more from the Screening visit should be reported as an adverse event. An adverse event of visual acuity will be counted from the following lines: 20/20 or better, 20/25, 20/30, 20/40, 20/50, 20/60, 20/70, 20/80, 20/100, 20/125, 20/150, and 20/200. If the acuity at screening is better than 20/20, then the decrease will be calculated from 20/20.

In the event of a decrease in visual acuity of 3 lines or more from screening, refraction should be rechecked.

Biomicroscopy

Slit-lamp biomicroscopy without dilation of the pupil will be performed a qualified practioner. Slit-lamp biomicroscopy should precede intraocular pressure (IOP) measurement and the administration of any pupil-dilating agent for ophthalmoscopy.

At each scheduled visit, any abnormalities of the lids, conjunctivae, cornea, anterior chamber, iris, or lens will be recorded at screening and any change from screening will be graded as mild, moderate, or severe. Aphakia or intraocular lens (anterior chamber intraocular lens, posterior chamber intraocular lens, or iris clip) and status of the posterior lens capsule (intact, open, or absent) should be specified. Cells and flare in the anterior chamber should be noted during the slit-lamp examination.

Table 7. Intraocular Inflammation Grading Scale for Biomicroscopy

	Grade				
	0	**1**	**2**	**3**	**4**
Grading of aqueous flare[a]	Completely Absent	Barely Detectable	Moderate (iris and lens details clear)	Marked (iris and lens details hazy)	Intense (formed fibrin in aqueous)
Grading of cells in the aqueous[a,b]	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

[a] Evaluation of Anterior Chamber Inflammation:
1. Examination of the anterior chamber for cells must be performed before either dilation or applanation tonometry.
2. The light intensity of the slit lamp is turned to the maximum tolerated by the patient.
3. High magnification and 1 x 2 mm slit are used.
4. The ray of light as directed at an angle of approximately 45° to the plane of the iris.

[b] Modified from Hogan MJ, Kimura SJ, Thygeson P: Signs and symptoms of uveitis: I. Anterior uveitis. Am J Ophthalmol 1959;47:155-70.

Ophthalmoscopy

Ophthalmoscopy will be performed after pupillary dilation to examine the vitreous body, retina macular, retina non-macula (peripheral), and optic nerve head.

For those patients who are selected for additional testing based on clinical judgment, the refractive error (sphere, cylinder, axis), pupillary size (millimeters), optical coherence tomographic central retinal subfield thickness (microns), and intraocular pressure (mm Hg) will be collected at screening and during the treatment period, and as clinically indicated.

7.2. Pharmacokinetics Assessments

Plasma samples will be obtained from all patients for PK analysis of axitinib and crizotinib (and its metabolite) depending on the treatment cohort that they belong to.

7.2.1. Blood Sample Collection for Pharmacokinetic Analysis

Where noted in the Schedule of Activities (SOA), blood samples will be collected at approximately the same time as other assessments wherever possible. Pharmacokinetic samples will be collected from all patients in the Dose Escalation Phase. In the Dose Expansion Phase, pharmacokinetic samples will be obtained from at least 8 evaluable patients in Cohort 1.

PK table indicates PK blood sampling time points for axitinib alone and axitinib in combination with crizotinib. On the days of sample collection, patients should be instructed to hold morning dosing until the pre dose sample has been drawn. Patients should have been taking axitinib uninterrupted for at least 3 days prior to each of the axitinib pharmacokinetic sample collection visits. For all collections, the time of dosing, as well as actual times of pharmacokinetic collections will be recorded in the source documents and CRF.

The pharmacokinetics of steady state axitinib alone will be evaluated on Lead-in Day 7. Pharmacokinetics of axitinib and crizotinib will be evaluated on Cycle 1 Day 15. The pharmacokinetics of crizotinib alone will be evaluated on Day 1 of Cycle 2, Cycle 3, Cycle 4 and Cycle 5.

Serial pharmacokinetic samples for axitinib will be collected on Lead-in Day 7 and Cycle 1 Day 15. Serial pharmacokinetic samples for crizotinib will be collected on Cycle 1 Day 15. On both days of serial pharmacokinetic sampling (Lead-in Day 7 and Cycle 1 Day 15), blood samples will be obtained at the following time points: predose, 1, 2, 3, 4, 6, and 8 hours after dosing. Additionally, predose samples for crizotinib will be collected on Day 1 of Cycle 2, Cycle 3, Cycle 4 and Cycle 5.

In addition to samples collected at the scheduled times, an additional blood sample should be collected from patients experiencing unexpected and/or SAE's and the date and time documented in the CRF.

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. 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.

PK samples will be assayed for axitinib, crizotinib and related metabolites using validated analytical methods in compliance with Pfizer standard operating procedures. Additional details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual.

7.2.2. Collection of Crizotinib PK Samples

At each time point for crizotinib, a 3 mL whole blood sample will be collected into an appropriately labeled K_2EDTA tubes to provide a minimum of 1 mL plasma for pharmacokinetic analysis.

7.2.3. Collection of Axitinib PK Samples

At each time point for axitinib, a 3 mL whole blood sample will be collected into an appropriately labeled K_3EDTA tubes to provide a minimum of 1 mL plasma for pharmacokinetic analysis.

7.2.4. Processing, Storage and Shipment of Crizotinib and Axitinib PK Samples

The following special precautions should be taken to minimize the rapid degradation of axitinib and crizotinib in plasma when exposed to visible light:

- Following collection of blood samples, samples should be processed as soon as possible. Preferably, harvested plasma should be frozen within 1 hour of collection.
- The blood collection tube should be gently inverted (8-10 times) to thoroughly mix the blood with the anti-coagulant.
- Vacutainer tubes should be protected from light (covered completely in aluminum foil or in black protection tubes) and placed in an ice-bath while samples are waiting to be centrifuged to harvest plasma.
- Following centrifugation (for at least 10 minutes at 1700 g at 4°C or lower), plasma should be transferred rapidly to labeled amber cryovials and stored at -20°C or lower.
- All samples should be transferred to an opaque box to protect from light exposure during storage and shipment. If a sample is inadvertently exposed to light (for 5 minutes or more), the sponsor should be notified so that the sample can be flagged for possibly spurious results.
- Once frozen, samples should not be allowed to thaw, including during shipment.

Samples will be shipped with the completed sample inventory form and sufficient dry ice to last for at least two days. Detailed instructions on sample collection, preparation, storage, and shipping will also be provided in the Study Manual.

Axitinib and crizotinib pharmacokinetic samples will be analyzed using separate validated analytical methods for each drug in compliance with Pfizer Standard Operating Procedures to determine plasma concentrations for axitinib, crizotinib and their metabolites. As part of the understanding of the pharmacokinetics of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for axitinib, crizotinib and their metabolites. The results of such analyses may be included in the clinical report.

7.3. 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 crizotinib when used in combination with a VEGF

inhibitor. In addition, analyses of sequentially obtained tissue and blood biomarkers will provide an opportunity to investigate potential mechanisms of resistance as well as pharmacodynamic markers that may further the understanding of the mechanistic effects of the drug combination being studied.

7.3.1. Archived Tumor Tissue and De Novo Tumor Biopsies

Tumor tissue from archived tissue samples and/or a de novo biopsy (see Section 6.1.1 and 6.1.2) will be used to analyze candidate DNA, RNA or protein markers for their ability to predict or identify those patients who are most likely to benefit from treatment with the study drugs. Markers that may be analyzed include, but may not be limited to, cMET gene mutation and gene amplification, PTEN mutation or deletion; c-MET, HGF, PBRM1 protein expression assessed by immunohistochemistry (IHC). Comparisons between de novo biopsies from RCC patients treated with one prior line of systemic therapy and archived tumor tissue obtained prior to the one line of systemic treatment will be made to investigate whether potential predictive markers represent intrinsic or acquired mechanisms of resistance.

7.3.2. Peripheral Blood

Blood samples for plasma and serum preparations will be obtained from all enrolled patients (in the Dose Escalation Phase and in the Dose Expansion Phase Cohort 1 and 2) to measure DNA, RNA or protein markers known or suspected to be of relevance to the mechanism of action, the development of resistance, or the identification of those patients who might benefit from treatment with axitinib and crizotinib combination. Markers that may be analyzed include, but may not be limited to, the soluble c-MET ectodomain, HGF, Ang 2, and miRNA signature. Samples should be obtained pre-dose and at the same time as PK samples whenever possible (see Schedule of Activities).

7.4. Banked Biospecimens

7.4.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected

computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key or any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the Investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the Investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical trial.

A 4 mL blood biospecimen **Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis)** will be collected at the Baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

7.4.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the Banked Biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to Pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimen specified in Markers of Drug Response Section will be used. Patients may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.5. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with suspected brain metastases. The CT scans should be performed with contrast agents unless contraindicated for medical reasons.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, and then every 8 weeks of combination treatment as specified in the Schedule of Activities (SOA), and whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from the treatment (if not done in the previous 8 weeks).

For patients with known or suspected bone metastases a bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT is required at screening. Repeat bone imaging is required 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 confirmation of response for patients who have bone metastases.

Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

Assessment of response will be made using RECIST version 1.1 (Appendix 2).

All patients' files and radiologic images must be available for source verification and for potential peer review.

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 adverse event 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 28 calendar days after the last administration of the investigational product. Serious adverse events 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 serious adverse events 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 one 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;
- Extravasation;
- 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.

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

An SAE 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 Section 8.14.1 on SAE 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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

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

    - For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT value ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- **Concurrent with**

    - For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (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 and for oncology studies, 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)/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 an 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 work-up 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;
- Pre-planned 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 non-invasive 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 4.0 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, a 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 serious adverse 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 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.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) 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 women (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 a Serious Adverse Event 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 termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure 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 serious adverse events when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy 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 Also the Section on Patient Withdrawal)

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 due to 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 timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational 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/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes 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

Adverse event 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 sets will be assessed.

- Safety analysis set.

The safety analysis set includes all enrolled patients who receive at least one dose of axitinib or crizotinib.

- Per protocol analysis set (evaluable for DLT).

All enrolled patients who are eligible, receive at least one dose of axitinib and crizotinib, and who either experience DLT during the first cycle, or complete the 1st cycle observation period. Patients who are lost to follow-up before receiving at least 75% of the planned first-cycle dose due to reasons unrelated to treatment related adverse events are not evaluable for DLT.

- Response evaluable analysis set.

All patients who start Cycle 1 with an adequate baseline tumor assessment and at least 1 follow up tumor assessment will be considered evaluable for anti-tumor efficacy using standard RECIST 1.1 criteria. Patients who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures.

- PK analysis set.

The PK concentration population is defined as all treated patients who have at least 1 concentration of any of the study drugs.

The PK parameter analysis population is defined as all treated patients who have at least 1 of the PK parameters of interest of any of the study drugs.

- Biomarker analysis set.

The biomarker analysis set is defined as all treated patients who have at least one screening biomarker assessment, and have received at least one dose of any study drug. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

If mutational profiling is performed on samples derived from the biomarker analysis set, the analysis may be limited to screening samples only.

9.2. Statistical Methods and Properties

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

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

The modified toxicity probability interval (mTPI) design[38] uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of three dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target rate (pT = 0.30). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

Being a model-based design, mTPI automatically and appropriately tailors dose-escalation and de-escalation decisions for different trials with different toxicity parameters. More importantly, all the dose-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table (Appendix 5). 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 I trial based on the mTPI design has been published.[39]

Decision rules are based on calculating unit probability mass (UPM) of three dosing intervals corresponding to under, proper, and over dosing in terms of toxicity. Specifically, the underdosing interval is defined as (0; pT-e_1), the over-dosing interval (pT+e_2), and the proper-dosing interval (pT- e_1, pT+ e_2), where e_1 and e_2 are small fractions. Based on the safety profile of axitinib and crizotinib, e_1 is selected as 0.05, and e_2 is selected as 0.00. Therefore, the target dosing interval for the DLT rate is (0.25, 0.30).

The three dosing intervals are associated with three different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (S). Given a dosing interval and a probability distribution, the unit probability mass (UPM) of that dosing interval is defined as the probability of a subject belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the three dosing intervals, and the one 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 under-dosing 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. Ji and collaborators[38] 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 dose-finding component of the trial is terminated when either approximately 25 DLT evaluable patients have been enrolled or when at least 10 evaluable patients have been treated at the highest dose with DLT rate <0.33, whichever comes first.

9.2.2. Statistical Method for Estimating the MTD

As described in Section 3.1.3, the estimated MTD will be the highest tested dose level with a DLT rate <0.33 in at least 10 DLT evaluable patients. We assume that higher doses of either axitinib or crizotinib result in higher toxicity rates. But, due to the relatively low number of patients that may be potentially allocated to any dose combination, this assumption may be violated.

For example, at the end of the study, the dose combination (crizotinib 250 mg BID, axitinib 3 mg BID) may have a higher proportion of observed toxicities than, say, (crizotinib 250 mg BID, axitinib 5 mg BID), and this variability may be simply related to small cohort size alone. To overcome this potential problem, we use a bivariate isotonic regression to smooth the resulting toxicity surface to a monotonically increasing one. The determination of the MTD contour is accomplished using the Dykstra-Roberston algorithm.[40] Once a monotonically increasing toxicity surface is obtained (either observed or smoothed according to the bivariate isotonic regression algorithm), the MTD combinations closest to the targeted DLT rate of 0.3 but still <0.33 are calculated. Clinical judgment will be exercised in taking forward combinations to the Expansion Phase cohort(s), in case no clear choice exists between more than 1 competing MTD combination. While the limited sample size may result in up to 2 dose combinations of equal potential anti-tumor activity, under the circumstances of this trial, likely only one will be chosen for the expansion cohort. This decision will be based upon the combination of data related to safety, anti-tumor activity, and clinical judgment of the Investigators and the Sponsor.

9.3. Sample Size Determination

The sample sizes planned for the study arise from logistic feasibility and past experience with Phase 1b studies in oncology and are not entirely driven by statistical considerations. It is expected that approximately 65 patients will be required to achieve all study objectives.

Due to the dynamic nature of the Bayesian allocation procedure, the sample size of the Up-and-Down matrix design using the mTPI approach cannot be determined in advance. It is estimated 25 DLT evaluable patients will be enrolled in the dose escalation stage in order to have a reliable and accurate estimate of the MTD. In addition, there will be Dose Expansion Phase cohorts to characterize safety, biomarkers, and efficacy in terms of probability (p) of achieving an event of interest including, but not limited to, objective response (OR). The goal will be to estimate proportions of such patients with the standard error (SE) of not greater than 0.12, ie, by definition,

$$SE = \sqrt{\frac{p(1-p)}{n}} \leq \frac{1}{2\sqrt{n}}$$

Therefore, a sample of twenty patients ($n=20$) per Dose Expansion Phase cohort will allow estimation of the probability of achieving an event of interest with the standard error <0.12.

9.4. Efficacy Analysis

In this study anti-tumor activity is a secondary objective. Efficacy analyses will be presented in the form of statistical summaries and data listing for the Dose Expansion Phase cohorts. For the Dose Escalation cohorts only data listings will be presented.

9.4.1. Analysis of Efficacy Endpoints (Dose Expansion Phase Cohorts)

Objective response rate (ORR) is defined as the proportion of patients with a confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 definitions, relative to the response evaluable population as well as the safety population. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR.

Duration of Response (DR) is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first.

Progression Free Survival (PFS) is defined as the time from the first dose to the first progression of disease (PD) or death for any reason in the absence of documented PD. PFS will be summarized in the safety analysis set. PFS data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study. Patients lacking an evaluation of tumor response after enrollment will have their PFS time censored on the date of first dose with a duration of 1 day. Patients who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as an event at the time of progression. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumor assessment prior to the start of the new therapy.

Summaries will include: ORR, DR and 6-month PFS probabilities. Time-to event endpoints (PFS and DR) will be analysed with Kaplan-Meier method. Point estimates will be presented with their 95% confidence intervals. In addition, progression date, death date, date of first response and last tumor assessment date will be listed, together with best overall response (BOR), DR and PFS.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetic Analysis of Crizotinib and Axitinib

All patients who complete at least one day of PK blood sampling will be included in the PK analyses. Standard plasma PK parameters for axitinib and crizotinib (and metabolite) will be estimated using non-compartmental analysis. For crizotinib, standard PK parameters will include the maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve to the time of the last measurable concentration ($AUC_{0\text{-}last}$), area under the plasma concentration versus time curve to 12 hours ($AUC_{0\text{-}12}$), and oral plasma clearance (CL/F). For axitinib, standard PK parameters will include C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}12}$, CL/F, apparent volume of distribution (V_z/F) and plasma elimination half life ($t_{½}$). Descriptive statistics for the PK parameters for each drug will be provided by day of assessment in tabular form.

All 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 the concentration-time data will be plotted by dose, cycle and day (single dose and steady-state) using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Trough concentrations for crizotinib will be plotted for each dose using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

In addition, Non-linear Mixed Effects Modeling (NONMEM) approaches will be explored to further describe the pharmacokinetic profile and assess potential drug interaction.

9.5.1.2. Effect of Crizotinib on Axitinib Pharmacokinetics

The effect of repeated crizotinib dosing on axitinib PK will be evaluated using AUC_{0-12} of axitinib on Lead-in Day 7 and Cycle 1 Day 15, respectively, as the primary pharmacokinetic parameter. Ninety-percent confidence interval for the ratio of geometric means of AUC_{0-12} (axitinib in presence of crizotinib/axitinib alone) will be computed to assess the magnitude of the effect.

9.5.1.3. Population Pharmacokinetic Analysis or PK/PD Modeling

Mechanism-based or semi-mechanistic sequential pharmacokinetic-pharmacodynamic models may be developed using NONMEM® to explore any relationships between plasma drug concentrations and selected safety, biomarker, and efficacy endpoints.

The results of these analyses, if performed, will be reported separately.

9.5.1.4. Statistical Analysis of Biomarker Endpoints

Biomarkers will be assessed separately for blood and tumor tissue samples. In each case, summaries of baseline levels and changes from baseline will be reported. Summary statistics may include the mean and standard deviation, median, and minimum/maximum levels of biomarker measures or frequency statistics, as appropriate.

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

Due to the exploratory nature of the proposed biomarkers, the data analysis will be conducted with the goal of identifying biomarkers with the strongest concordance to clinical outcome, encompassing both safety and efficacy. Candidate biomarkers will be validated in subsequent trials.

9.6. Safety Analysis

Summaries and analyses of the primary safety endpoint will be based on the per protocol analysis set. All other summaries and analyses of safety parameters will include all patients in the Safety Analysis Set. Safety data will be summarized by each cohort for all treated patients using appropriate tabulations and descriptive statistics. Safety data collected during the lead-in PK period will be reported separately. The analysis of safety will extend through 28 days after the last administration of study drug.

9.6.1. Analysis of Primary Safety Endpoint

Dose Limiting Toxicity (DLTs) is the primary endpoint of the Dose Escalation Phase of the study. The occurrence of DLTs observed in the Dose Escalation Cohorts is used to estimate the MTD (if reached) as described in Section 3.1.3. Adverse Events constituting DLTs will be listed per cohort.

9.6.2. Analysis of Secondary Safety Endpoints

9.6.2.1. Adverse Events

Adverse Events (AEs) will be graded by the Investigator according to the Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 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 medication. The number and percentage of patients who experienced any AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

9.6.2.2. Laboratory Tests Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each lab assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

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

9.6.2.3. ECG

All ECGs obtained during the study will be evaluated for safety. The triplicate ECG data will be averaged. All summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Any data obtained from hand-reading of abnormal ECGs by a cardiologist (reported as unplanned ECGs in CRF) will be averaged separately and reported in summary tables, although both cardiologist manual overreads and machine-calculated values for the same time points will be provided in data listings. QT measurements corrected by heart rate (QTc) using Bazett's (QTcB) and Fridericia's (QTcF) methods will be used for the data analysis and interpretation.

9.6.3. Concomitant Medications/Follow-up Systemic Therapy

All medications received during the treatment period will be considered as concomitant medications and will be coded by WHO medical dictionary. Patients who received concomitant medications will be listed. Follow-up systemic therapy for the primary diagnosis will be summarized by categories of follow-up therapy and will be listed for each patient as appropriate.

9.6.4. Ophthalmologic Data

Best corrected visual acuity (Snellen fraction), biomicroscopic, and ophthalmoscopic findings will be recorded at baseline and any change from baseline will be summarized/listed for all patients who receive a dose of study treatment, with a baseline assessment and at least one post-baseline assessment.

For those patients who are selected for additional testing based on clinical judgment, the refractive error (sphere, cylinder, axis), pupillary size (millimeters), optical coherence tomographic central retinal subfield thickness (microns), and intraocular pressure (mm Hg) at screening and their changes from screening will be quantitatively summarized/listed. The qualitative findings of fundus photography and optical coherence tomography at screening and their changes from screening will also be summarized/listed.

For the baseline screening results, percentages of patients falling into each category of the examination status (normal, mild, moderate, or severe) will be summarized/listed for each structure by eye. For post-baseline results, percentages of patients falling into each category of the examination status (new findings/worsening of finding, no change, improvement of finding, etc.) will be summarized/listed for each eye structure.

Additional summaries of ophthalmologic data will be considered as appropriate and described in the SAP.

9.7. Data Monitoring Committee

An external Data Safety Monitoring Committee will not be established for the 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 include:

- Surveillance for SAEs according to regulatory guidelines.
- Discussions between the Investigators and the Sponsor of AEs, laboratory tests abnormalities, vital signs and ECGs findings observed at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and make risk/benefit assessment and decide if further enrollment is appropriate. During the Dose Escalation Phase, in particular, monitoring and safety findings satisfying the DLT criteria will be discussed in an on-going manner.

- Findings having immediate implication for the management of patients on study will be communicated to all Principal Investigators in the timeframe associated with unexpected and drug-related SAEs.

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 is 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 patient to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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 is true. Any corrections to entries made in the CRFs, 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 Investigator's 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, telephone calls reports). The records should be retained by the Investigator according to International Conference on Harmonisation (ICH), 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 (IRB)/Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

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

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

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient 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 ethics committees and Investigator databases may be used as recruitment procedures.

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 which 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 is defined as the time at which it is deemed that sufficient 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 Subject 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/IEC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of axitinib or crizotinib 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 trial concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European (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, 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.

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, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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 multi-centre study, 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, Investigator is free to publish separately, patient 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. 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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2. RECIST 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 8 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 8 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 3. 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

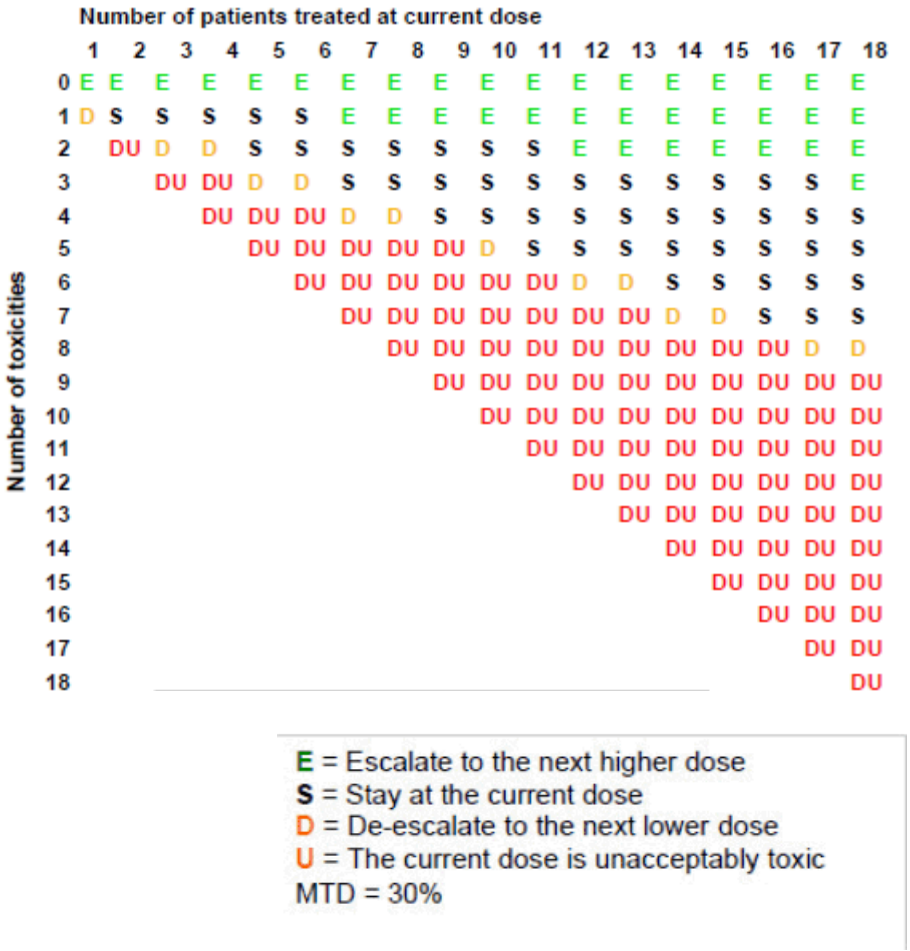
Appendix 4. Abbreviations and Definitions of Term

AE	Adverse Event
AHFS	American Hospital Formulary Service
AIDS	Acquired Immune Deficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ATP	Adenosine TriPhosphate
ASHP	American Society of Hospital Pharmacists
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BAL	BronchoAlveolar Lavage
BCVA	Best Corrected Visual Acuity
BHD	Birt-Hogg-Dubé
BID	Twice/day
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Clearance
Cmax	Maximum plasma Concentration
Cmin	Minimum plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRPC	Castration-Resistant Prostate Cancer
CSA	Clinical Study Agreement
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events (US-NCI)
CTM	Clinical Trial Material
CYP1A2	Cytochrome P450 enzyme-1A2
CYP3A4/5	Cytochrome P450 enzyme-3A4/5
DLT	Dose Limiting Toxicity
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
EDP	Exposure During Pregnancy
EIU	Exposure in Utero
EU	Europe
FDA	Food and Drug Administration
^{18}F FDG PET/CT	2-[18F]-fluoro-2-deoxy-d-glucose Positron emission tomography/ computed tomography
FFPE	Formalin Fixed, Paraffin Embedded
FH	Fumarate Hydratase

FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HDPE	High Density PolyEthylene
HGF	Hepatocyte Growth Factor
HIF	Hypoxia-Inducable transcription Factor
HIV	Human Immunodeficiency Virus
ICH	International Committee Harmonization
ID	Identification
IEC	Independent Ethics Committee
IFN	Interferon alpha
IL-2	Interleukin-2
IHC	ImmunoHistoChemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IOP	IntraOcular Pressure
IRB	Institutional Review Board
IUD	Intra Uterine Device
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal Epithelial Transition factor
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target Of Rapamycin
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NONMEM	Non linear Mixed Effects Modeling
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic
PD	Progressive Disease
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PFS	Progression Free Survival
PK	Pharmacokinetics
PO	Per Os (by mouth)
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QD	Every Day
QTc	Corrected Q-T interval
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event

SD	Stable Disease
SD	Standard Deviation
SRSD	Single Reference Safety Document
t½	Plasma elimination half life
TKI	Tyrosine Kinase Inhibitor
Tmax	Time to maximum plasma concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
USPI	United States Package Insert
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VHL	Hippel Lindau tumor suppressor gene
WBC	White Blood Cell
WHO	World Health Organization

Appendix 5. Detailed Dose Escalation/De-Escalation Scheme



E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 30%

Escalation/De-escalation algorithms for total number of patients treated at the current dose level (current and previous cohorts)

- With 3 patients treated at current dose level
  - 0 DLT → escalate
  - 1 DLT → remain at the same dose
  - 2 DLTs → de-escalate
  - 3 DLTs → de-escalate and consider current dose as intolerable
- With 4 patients treated at current dose level
  - 0 DLT → escalate
  - 1 DLTs → remain at the same dose

    - 2 DLTs → de-escalate
    - 3-4 DLTs → de-escalate and consider current dose as intolerable
- With 5 patients treated at current dose level
    - 0 DLT → escalate
    - 1-2 DLTs → remain at the same dose
    - 3 DLTs → de-escalate
    - 4-5 DLTs → de-escalate and consider current dose as intolerable
- With 6 patients treated at current dose level
    - 0 DLT → escalate
    - 1-2 DLTs → remain at the same dose
    - 3 DLTs → de-escalate
    - 4-6 DLTs → de-escalate and consider current dose as intolerable
- With 7 patients treated at current dose level
    - 0-1 DLT → escalate
    - 2-3 DLTs → remain at the same dose
    - 4 DLTs → de-escalate
    - 5-7 DLTs → de-escalate and consider current dose as intolerable
- With 8 patients treated at current dose level
    - 0-1 DLT → escalate
    - 2-3 DLTs → remain at the same dose
    - 4 DLTs → de-escalate
    - 5-8 DLTs → de-escalate and consider currentdose as intolerable

- With 9 patients treated at current dose level
    - 0-1 DLT → escalate
    - 2-4 DLTs → remain at the same dose
    - 5-9 DLTs → de-escalate and consider currentdose as intolerable
- With 10 patients treated at current dose level
    - 0-1 DLT → escalate
    - 2-4 DLTs → remain at the same dose
    - 5 DLTs → de-escalate
    - 6-10 DLTs → de-escalate and consider currentdose as intolerable
- With 11 patients treated at current dose level
    - 0-1 DLT → escalate
    - 2-5 DLTs → remain at the same dose
    - 6-11 DLTs → de-escalate and consider currentdose as intolerable
- With 12 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-5 DLTs → remain at the same dose
    - 6 DLTs → de-escalate
    - 7-12 DLTs → de-escalate and consider current dose as intolerable
- With 13 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-5 DLTs → remain at the same dose
    - 6 DLTs → de-escalate
    - 7-13 DLTs → de-escalate and consider current dose as intolerable

- With 14 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-6 DLTs → remain at the same dose
    - 7 DLTs → de-escalate
    - 8-14 DLTs → de-escalate and consider current dose as intolerable
- With 15 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-6 DLTs → remain at the same dose
    - 7 DLTs → de-escalate
    - 8-15 DLTs → de-escalate and consider current dose as intolerable
- With 16 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-7 DLTs → remain at the same dose
    - 8-16 DLTs → de-escalate and consider current dose as intolerable
- With 17 patients treated at current dose level
    - 0-2 DLTs → escalate
    - 3-7 DLTs → remain at the same dose
    - 8 DLTs → de-escalate
    - 9-17 DLTs → de-escalate and consider current dose as intolerable
- With 18 patients treated at current dose level
    - 0-3 DLTs → escalate
    - 4-7 DLTs → remain at the same dose
    - 8 DLTs → de-escalate
    - 9-18 DLTs → de-escalate and consider current dose as intolerable