CLINICAL PROTOCOL

A PHASE 1B, OPEN LABEL, DOSE FINDING STUDY TO EVALUATE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AXITINIB (AG-013736) IN COMBINATION WITH PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH ADVANCED RENAL CELL CANCER

Compounds:	AG-013736, MK-3475
Compound Names:	Axitinib, MK-3475
US IND Numbers:	CCI [redacted]
Protocol Number:	A4061079
Phase:	1b

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 2	03 April 2018	Removed most of the efficacy assessments after completing collection of data for the primary and most secondary endpoints (see Appendix 6). Administrative changes to sections such as banked biospecimens, adverse events, drug storage, and patient informed consent to align with latest Pfizer protocol template. Further clarified dose modification sections and updated with new MK-3475 safety and management of toxicities guidelines.
Amendment 1	18 March 2015	Changed dose level -1 to axitinib 3 mg bid and MK-3475 to 2 mg/kg every 3 weeks to allow testing a lower dose level of axitinib while MK-3475 dose remains at 2 mg/kg. Updated the protocol with new MK-3475 safety and management of toxicities guidelines. Updated the protocol template with the updated Pfizer protocol template language. Corrected typographical errors and improved consistency across the document.
Original protocol	20 March 2014	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).

PROTOCOL SUMMARY

Background and Rationale:

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults.[1] Until 2005, interferon-alpha (IFN-α) and high-dose interleukin (IL)-2 therapies were the standard of care for patients with advanced RCC (aRCC), albeit with modest efficacy. Since then, development and approval of multiple vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors have significantly improved the outcomes of aRCC patients. These agents include the VEGF receptor (VEGFR) tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, axitinib and sorafenib; the mTOR inhibitors temsirolimus and everolimus, and the anti-VEGF monoclonal antibody bevacizumab. However, despite the substantial improvement of patient outcomes with these agents, durable and complete response in aRCC patents are uncommon; the majority of patients will eventually develop resistance exhibit disease progression while on therapy and succumb to death due to metastatic disease.

There is a strong rationale for considering immunotherapy in aRCC patients. Cytokine-based immunotherapy, especially high-dose IL-2, exhibited durable responses in some aRCC patients. There are anecdotal reports of spontaneous remissions in aRCC patients with evidence of antigen-specific lymphocyte infiltration in tumor tissues.[2] These reports have generated considerable interest in immunotherapeutic approaches in the treatment of aRCC patients, especially with advent of immune-check point inhibitors such as anti-PD1 and anti-PD L1 antibodies in recent years. Upregulation of programmed death-1 (PD-1) receptor on tumor-infiltrating lymphocytes (TILs), and its ligand PD-L1 on tumors, are associated with more aggressive disease and poor prognosis.[3,4]

Blocking the PD-1/PD-L1 interaction is a novel immunotherapeutic approach for aRCC which has shown single-agent efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy.[6,7] BMS-936558, also named nivolumab, is a fully humanized anti-PD-1 antibody (Bristol-Myers Squibb) that has shown anti-tumor activity in 296 patients with solid cancers.[5.] Among these 296 patients, 33 patients had aRCC and were heavily pretreated before nivolumab therapy. Nivolumab was given at a starting dose of 1 mg/kg and then expanded to 10 mg/kg. The objective response rate (ORR) was 27% (9/33) and another 9 patients (27%) had stable disease at the 24-week follow-up time-point. Five patients had durable response longer than 1 year.[5] MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It is proposed in this study that the addition of the PD-1 inhibitor, MK-3475, to the VEGF pathway inhibitor axitinib may provide additional clinical benefit compared to treatment with axitinib alone.

Antitumor activity of single agent axitinib in treatment-naïve patients with clear cell aRCC was assessed against sorafenib in a randomized, open-label, Phase 3 trial. Although the study did not demonstrate a statistically significant difference in median PFS (mPFS) between patients treated with axitinib or sorafenib, axitinib was associated with a longer mPFS value {median PFS of 10.1 months (95% CI 7.2,12.1) with axitinib vs. 6.5 months (95% CI 4.7, 8.3) with sorafenib, stratified hazard ratio 0.77, (95% CI 0.56, 1.05)}. The

mPFS observed with axitinib in this study was similar to that demonstrated earlier in Phase 3 clinical trials with other approved VEGF TKIs in the first-line treatment of aRCC patients.[8] Toxicities in this clinical trial were manageable and similar to those observed in clinical trials with axitinib in pre-treated aRCC patients.[9]

This data supports the testing of MK-3475 in combination with axitinib in the first-line treatment of aRCC patients. The primary objective of this study will be to assess the safety and tolerability of the combination regimen in previously untreated aRCC patients. Secondary objectives of this study will include the assessment of objective response rate (ORR) and duration of response (DR); progression-free survival (PFS); overall survival (OS) up to five years. In addition, secondary objectives will also include pharmacokinetics (PK) of axitinib and MK-3475 when administered in combination and the effect of MK-3475 on the PK of axitinib and translational component. Specifically, assessments in tumor and/or blood will include characterization of drug target pathways (eg, PD-L1), and gene expression profiles.

Once the tolerability of the combination has been confirmed, a preliminary assessment of its antitumor activity will be conducted in an expansion cohort of aRCC patients in the first-line treatment setting.

Study Objectives:

Primary Objective

- To assess the safety and tolerability of axitinib in combination with MK-3475 in patients with previously untreated advanced RCC in order to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile of axitinib in combination with MK-3475.
- To assess the anti-tumor activity of axitinib in combination with MK-3475 in patients with advanced RCC in the first-line treatment setting.
- To characterize the pharmacokinetics (PK) of axitinib and axitinib plus MK-3475 when administered in combination, and to assess the effect of MK-3475 on the PK of axitinib.
- To characterize, using translational approaches, genes and proteins such as PD-L1, VEGF-A and IL-8 relevant to angiogenesis drug target pathway, renal cell carcinoma biology, and sensitivity/resistance mechanisms to axitinib in combination with MK-3475 in tumor and/or blood.
- To explore the pharmacodynamic effect of axitinib in combination with MK-3475 in blood and tumor by assessment of gene, RNAs and proteins including but not limited to VEGF-A, IL-8 and VEGFR2 and T-cell receptors.

- To assess the immunogenicity of MK-3475.

Study Design:

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of axitinib in combination with MK-3475 in adult patients with previously untreated advanced RCC. This clinical study will be composed of a Dose Finding Phase and a Dose Expansion Phase. The Dose Finding Phase will estimate the MTD in patients with advanced RCC patients with clear cell histology who did not receive prior systemic therapy for the advanced disease, using the modified toxicity probability interval (mTPI) method.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for axitinib in combination with MK-3475 in patients with aRCC who did not receive prior systemic therapy. The Expansion Test Dose will be either the MTD (ie, the highest dose of axitinib and MK-3475 associated with the occurrence of DLTs in <33% of patients) or the RP2D, 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 MK-3475 will be tested in patients with previously untreated aRCC. Approximately 60 patients (including Dose Finding Phase and Dose Expansion Phase) are expected to be enrolled in the study.

Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, 12 weeks, and every 6 weeks thereafter, using RECIST version 1.1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). Brain CT or MRI scans are required at baseline and when there is a suspected brain metastasis. Bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT is required at baseline then every 12 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.

If radiologic imaging shows progressive disease (PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD. Assigned study treatment may be continued at the investigator's discretion while awaiting radiologic confirmation of progression. If PD is confirmed (Section 5.2.4.2.1) patients may be discontinued from study treatment. However, if a patient with evidence of PD is still experiencing clinical benefit according to the investigator's judgment, he/she may be eligible for continued treatment with one or both study drugs (after discussion between the investigator and the Sponsor). The details of the criteria for study drug continuation in these patients are described in the Sections 3.1 and 5.2.4.2.1.

Discontinuation from MK-3475 treatment may be considered at the investigator's discretion for patients who have attained a confirmed CR, that have been treated for at least 24 weeks with MK-3475 and have received at least two treatments with MK-3475 beyond the date the initial CR was declared. Axitinib may be continued in those patients. Patients who then experience radiologic disease progression will be eligible for re-treatment with MK-3475 at

the discretion of the investigator if no cancer treatment was administered other than study drugs since the last dose of MK-3475, the patient meets the safety parameters listed in the Inclusion /Exclusion criteria and the trial is open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation. MK-3475 treatment will be administered for up to one additional year.

Patients will be monitored closely for toxicity and in the event of significant toxicity dosing may be delayed and/or reduced (Section 5.2.7). Based on the known safety profile of axitinib, blood pressure as well as thyroid function will be monitored throughout the treatment period. Based on data emerging from trials of VEGF tyrosine kinase inhibitors given in combination with PD-1 inhibitors, liver function tests will be monitored closely for the first 3 cycles.[49] MK-3475 dose modification and supportive care for drug related toxicities, including immune-related adverse events (irAEs) Section 5.2.7.4. 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).

Intra-patient dose escalation for axitinib is permitted only after completing 12 weeks of treatment if the starting dose of axitinib is 5 mg BID (DL1), and after 6 weeks if axitinib starting dose is 3 mg BID (DL-1) (Section 5.2.7).

MK-3475 and axitinib do not have competing elimination/metabolism pathways, hence an overt PK interaction between the two drugs is not anticipated. However, pharmacokinetic assessments will be conducted in this study to confirm the absence of drug-drug interactions. To understand the PK effects of MK-3475 on axitinib, a 7-day lead-in period with single-agent axitinib will be included prior to Cycle 1 in all patients in the Dose Finding Phase and in at least 8 patients in the Dose Expansion Phases of the study. On the contrary, the administration of single agent MK-3475 to this patient population is not considered in this trial. The effect of axitinib on MK-3475 will be evaluated by comparing MK-3475 trough concentrations at steady-state in the presence of axitinib with those reported for MK-3475 alone in prior studies. MK-3475 has a long half-life (21-28 days) and an increase in trough concentration over time is expected.

Archived tumor biospecimens, and baseline de novo biospecimens from metastatic lesions will be collected for all patients in the dose expansion cohort. Every effort will be made to obtain a second biopsy at the time of first tumor assessment at 12 weeks. Biomarker studies on tumor and blood biospecimens will be carried out to help understand the mechanism of action of the axitinib plus MK-3475 combination, as well as potential mechanisms of resistance. Such results may help in the future development of this combination. Analyses using translational approaches may also result in the identification of potential biomarkers of response to the axitinib plus MK-3475 combination, ultimately leading to the development of a patient selection strategy for further clinical investigation. As such, collection of tumor and blood biospecimens at baseline and on study will be of paramount importance.

After the collection of data for the primary study objective and most of the secondary objectives has been completed, this study (A4061079) will remain open to give patients an opportunity to continue to receive study treatment as described in Section 3 of this protocol. Guidance on the management of patients who continue on study (ie, patients who are still clinically benefiting from study treatment without unacceptable toxicity or disease progression and who have not withdrawn consent) is provided to investigators in Appendix 6. Clinical assessments will be reduced in scope and the required schedule of activities will be revised to maintain only those assessments that protect the well-being of the patient.

Study Treatment:

Axitinib will be given orally (PO) twice daily (BID) on a continuous dosing schedule. MK-3475 will be given as 30-minute intravenous infusion every 3-weeks. In all patients, treatment with study drugs will continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, whichever occurs first, or the study is terminated by the Sponsor (see Section 6.4, Patient Withdrawal).

The treatment duration with MK-3475 is 24 months calculated from the date of the first dose of MK-3475. Continuation of treatment with MK-3475 beyond 24 months should be discussed with the sponsor and not go beyond 36 months. Patients who stop MK-3475 for reasons other than confirmed disease progression may continue on treatment with axitinib single agent until disease progression (RECIST v. 1.1), patient refusal, unacceptable toxicity or the study is prematurely terminated by the Sponsor; whichever comes first.

Statistical Methods:

Up-and-Down Design with the mTPI Method

The escalation/de-escalation rules will follow the modified toxicity probability interval (mTPI) method. 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 when 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 at each dose level will initiate dosing sequentially, at least 2 days apart, to allow for the initial evaluation of toxicities and tolerability. If the first 2 patients experience a DLT prior to enrollment of the third, the dose level will be deemed intolerable the dose level will be de-escalated. 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 (target 3 patients) can be enrolled when all patients at the current dose cohort have been evaluated for 6 weeks (ie, the first two treatment cycles), or experience a DLT, whichever comes first.

- If a patient withdraws from study treatment before receiving at least 75% of the planned first two cycles (6 weeks) doses of axitinib or two infusions of MK-3475 within the DLT observation period for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.

- The dose-finding component of the trial is completed when at least 10 DLT-evaluable patients have been treated at the highest dose associated with a DLT rate <0.33. It is estimated that approximately 20 DLT-evaluable patients will need to be enrolled to reach 10 DLT-evaluable patients at the estimated MTD.

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

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 design using the mTPI approach cannot be determined in advance. It is estimated that 20 DLT-evaluable patients will be enrolled in the Dose Finding Phase in order to have a reliable and accurate estimate of the MTD. The expansion cohort will enroll up to 40 patients at the estimated MTD. The sample size estimate for the expansion cohort takes into consideration the key tumor biomarker PD-L1 endpoints and historical data assuming 20% of RCC patients as tumor PD-L1 positive: if the observed rate of tumor PD-L1 positives patients is 20% then approximately 40 patients would be required to enroll 8 PD-L1 tumor positive patients.

Dose Finding Criteria:

Dose escalation and de-escalation will follow an "Up-and-Down" design, using doses of MK-3475 and axitinib as shown in the Dose Levels in Dose Finding Phase Table 1.

Dose Levels in Dose Finding Phase

Dose Level	MK-3475	Axitinib
1 (Starting Dose Level)	2 mg/kg IV q3wk	5 mg BID
-1	2 mg/kg IV q3wk	3 mg BID

BID: twice daily; q3wk: every 3 weeks

Dose level (DL) -1 will be explored only if the MTD is already exceeded at DL1.

Alternative doses, schedule(s) and PK time points may be considered during the study based on the emerging safety and PK data.

SCHEDULE OF ACTIVITIES

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

The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities, in order to conduct evaluations or assessments required to protect the well-being of the patient. Please refer to Appendix 6 for a revised Schedule of Activities associated with Amendment #2.

SCHEDULE OF ACTIVITIES

Protocol Activities[1]	**Screening**	**Lead-in PK Period**[2]		**Study Treatment (1 cycle = 21 days)**			**Post-Treatment**	
				Cycle 1		**Cycles ≥2**		
	≤28 Days Prior to Registration	**Day 1 (±2 days)**	**Day 7**	**Day 1 (±3 days)**	**Day 5 (±2 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	
ECOG Performance Status	X	X		X		X	X	
In Clinic Blood Pressure, Pulse Rate[9]	X	X	X	X		X	X	
Home Blood Pressure Monitoring [10]	X	X						
Follow-up for Axitinib Dosing Compliance [11]					X	As needed based on axitinib dose modifications		
Laboratory Studies								
Hematology[12]	X	(X)		X		X	X	
Blood Chemistry[12]	X	(X)		X		X	X	
Coagulation[12]	X	(X)		X		X	X	
Urinalysis[13]	X	(X)		X		X	X	
12-lead ECG[14]	X			X			X	
Thyroid Function Tests [15]	X	(X)		X		X		
Pregnancy Test [16]	X	X		X		X	X	
Disease Assessments								

Protocol Activities[1]	**Screening**	**Lead-in PK Period**[2]		**Study Treatment (1 cycle = 21 days)**			**Post-Treatment**	
				Cycle 1		**Cycles ≥2**		
	≤28 Days Prior to Registration	**Day 1 (±2 days)**	**Day 7**	**Day 1 (±3 days)**	**Day 5 (±2 days)**	**Day 1 (±3 days)**	**End of Treatment /Withdrawal (±3 days)**[3]	**Follow-up Day 28 (+7 days) After Last Dose**[4]
Tumor Assessments (including scans)[17]	X					X (at 12 weeks and then every 6 weeks)	X	
Other Clinical Assessments								
Adverse Events[19]		X						
Survival[18]								X
Concomitant Medications/Treatments[20]	X	(X)	X	X		X	X	X
Registration and Study Treatment [21]								
MK-3475[22]				X[22]		X[22]		
Axitinib[22]		X						
Other Samplings								
Pharmacokinetics[23]			X	X	X	X (Cycles 3, 5, 7, 11 and then q12w)		
Serum Biomarkers[24]	X					X (Cycle 2 only)	X	
Whole Blood Biomarkers[25]	X					X (Cycle 2 only)	X	
Banked Biospecimen[26]	X							
Archival Tumor Tissue[27]	X							
De Novo Tumor Biospecimen[28]	X					X[28]		
Anti-MK-3475 Antibodies[29]				X		X[29]		X[29]

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.
2. **Lead-in PK Period:** All patients in the Dose Finding Phase, and at least 8 patients in the Dose Expansion Phase.
3. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessment which need not be repeated if performed within the prior 6 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. See footnote 19 and Section 8.1.1.
5. **Informed Consent:** Must be obtained prior to undergoing any trial specific procedure.
6. **Medical/Oncological History:** To include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery and radiation therapy.
7. **Baseline Signs/Symptoms:** To be documented and recorded at Lead-in Day 1 or Cycle 1 Day 1 predose for all patients.
8. **Physical Examination:** Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at screening only).
9. **In Clinic 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:** All patients will receive home blood pressure monitoring devices and blood pressure will be monitored at home. While on axitinib (as single agent during the Lead-in, or combined with MK-3475) patients 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 5.2.7.3).
11. **Follow-up for Dosing Compliance:** Follow-up by telephone will be done to confirm patient understanding and compliance with dosing instructions. If needed, patient will be retrained.
12. **Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 8. Blood Chemistry may be performed weekly during the first 3 cycles. All laboratory tests may be performed also when clinically indicated. Dose adjustment may be required (see Section 5.2.7).
13. **Urinalysis (**Table 8): 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 5.2.7.2). May be performed also when clinically indicated.
14. **12-lead ECG**: See Section 7.1.5 for details. Single ECG measurement will be obtained at screening, on Cycle 1 Day 1 and End of Treatment/Withdrawal. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. Additionally, ECGs should be performed when clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
15. **Thyroid Function Tests:** Free T3, free T4 and TSH will be performed at baseline/screening, Lead-in Day 1; or at baseline (Cycle 1 Day 1 pre-dose for patients with no lead in dose or within 7 days of Cycle 1 Day 1) for all patients. Subsequently, TSH should be assessed at Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, and every 6 weeks thereafter starting from Cycle 8 Day 1. Free T3 and free T4 should additionally be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.

16. **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 therapy: 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 MK-3475. Following a negative pregnancy result at screening, appropriate contraception must be commenced. Pregnancy tests will also be routinely repeated at every 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. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations (see Section 7.1.1).
17. **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 scans (required at baseline and when suspected brain metastasis) and bone scans (required at baseline then every 12 weeks only if bone metastases are present at baseline) see Section 7.5. 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, 12 weeks then every 6 weeks, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). Follow up bone scans is required every 12 weeks only if bone metastases are present at baseline. Otherwise bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of response for patients who have bone metastases. Assessment of response will be made using RECIST version 1.1.
18. **Survival:** All patients should be followed for survival at least every 3 months after discontinuing study treatment. Survival monitoring will continue until 5 years after Cycle 1 Day 1 of the last patient enrolled in the study.
19. **Adverse Events:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product and before initiation of a new anti-cancer treatment. The prolonged follow up is due to the pharmacokinetic properties of the investigational product MK-3475. SAEs experienced by a patient after the active reporting period (see Section 8.1.1) 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 study drug 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. Pregnancy or breast feeding that occur during the trial, within 120 days of discontinuing treatment with MK-3475, or within 28 days after the cessation of study treatment if the patient begins a new anticancer therapy, whichever is earlier, should be reported as in Section 8.4 (Exposure During Pregnancy).
20. **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).
21. **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 MK-3475 for all other patients) should begin within 7 days of registration.
22. **Study Treatment:** Axitinib will be given orally twice daily PO on a continuous schedule. MK-3475 will be given as a 30-minute intravenous infusion every 3 weeks. (one Cycle = 3 weeks) (see Section 5). Patients with disease progression who are continuing to derive clinical benefits from the study treatment will be eligible to continue with study drugs provided that the treating physician has determined that the benefit/risk for doing so is favorable.

23. **Pharmacokinetics**: Samples will be collected at the time points indicated in the Schedule for Pharamcokinetic Samples Collection Table. Pharmacokinetic samples for MK-3475 will be collected from all patients in the study. Pharmacokinetic samples for axitinib will be collected from all patients in the Dose Finding Phase and at least 8 patients in the Dose Expansion Phase. Details are outlined in Section 7.2.
24. **Serum Biomarkers**: Blood biospecimens (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 MK-3475. Blood biospecimens will be collected at screening, Cycle 2 Day 1 predose, and End of Treatment/Withdrawal whichever comes first. See Section 7.3.2.
25. **Whole Blood Biomarkers**: Blood biospecimen (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 MK-3475. Blood samples will be collected at screening, Cycle 2 Day 1 predose, and End of Treatment/Withdrawal whichever comes first. See Section 7.3.2
26. **Banked Biospecimen:** A single 4 mL blood sample will be collected at screening. Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (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/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study. Banked biospecimens retained in the BBS also can be used in research on RCC. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision. See Section 7.4.
27. **Archival Tumor Tissue:** Mandatory Archival Biospecimen from primary diagnosis for all patients enrolled in the study (Dose Finding and Dose Expansion Phases). Formalin-fixed, paraffin-embedded (FFPE) block(s) from initial diagnosis. If no FFPE block is available, then at least 12 unbaked, unstained slides containing FFPE tissue sections that are 4 microns (preferred) or 5 microns (acceptable) thick must be provided. However FFPE blocks are strongly encouraged over slides. See Section 7.3.1.
28. ***De Novo* Tumor Biospecimens:** Baseline *de novo* tumor biospecimens from metastatic tumor sites are mandatory for all patients enrolled in the Dose Expansion Phase. Baseline *de novo* tissue biopsies taken from metastatic lesions prior to the date of screening are acceptable. For all patients in the Dose Expansion cohort, a second biopsy is strongly encouraged at the time of first tumor assessment after 12 weeks. If possible the tumor biospecimen at 12 weeks should come from the same baseline anatomical location. Formalin-fixed, paraffin-embedded (FFPE) block(s) of metastatic lesion tumor biospecimens from baseline *de novo* biopsies that contain sufficient tissue to generate at least 12 unstained slides are required, each with tissue sections that are 5-microns thick. If no FFPE block is available, then at least 12 unbaked, unstained slides containing FFPE tissue sections that are 5 microns thick must be provided. However FFPE blocks are strongly encouraged over slides. See Section 7.3.1.
29. **Anti-MK-3475 Antibodies (anti-drug antibodies, ADA):** One blood sample (6 mL) for anti-MK-3475 antibodies will be collected pre-dose on Cycle 1, 3, 5 and 11. Subsequently, testing should be performed approximately every 12 weeks. All samples should be drawn within 24 hours before start of MK-3475 infusion. Additional samples for anti-MK-3475 antibodies (and simultaneous pharmacokinetic draws for measurement of MK-3475) will be collected at 30 days, 3 months and 6 months after the end of MK-3475 treatment. See Section 7.2.5.
a. (X) = only if activity not performed in prior 7 days.

SCHEDULE FOR PHARMACOKINETIC SAMPLE COLLECTION

Axitinib	**Axitinib in Combination with MK-3475**							
Lead-in Day7	**Cycle 1**			**Cycles 3 and 5**		**Cycle 7**	**Cycle 11 and every 12 weeks thereafter**	
	Day 1		**Day 5**	**Day 1**		**Day 1**	**Day 1**	
PK Samples for axitinib[a]	**PK Samples for MK-3475[b]**	**Sample for anti-MK-3475-antibodies (ADA)[c]**	**PK Sample for MK-3475[b]**	**PK Sample for MK-347[b]**	**Sample for anti-MK-3475-antibodies (ADA)[c]**	**PK Samples for axitinib[a]**	**PK Sample for MK-3475[b]**	**Sample for anti-MK-3475-antibodies (ADA)[c]**
Prior to axitinib morning dose	Prior to MK-3475 dose	Prior to MK-3475 dose	One sample collected at any time between Cycle 1 Day 3 and Cycle 1 Day 7 for MK-3475; the exact time/day of sample collection to be noted in Case Report Form.	Prior to MK-3475 dose	Prior to MK-3475 dose[c]	Prior to axitinib morning dose	Prior to MK-3475 dose	Prior to MK-3475 dose
1 hr post axitinib morning dose	End of MK-3475 infusion[d]					1 hr post axitinib morning dose		
2 hrs post axitinib morning dose						2 hrs post axitinib morning dose		
3 hrs post axitinib morning dose						3 hrs post axitinib morning dose		
4 hrs post axitinib morning dose						4 hrs post axitinib morning dose		
6 hrs post axitinib morning dose						6 hrs post axitinib morning dose		
8 hrs post axitinib morning dose						8 hrs post axitinib morning dose		

K= pharmacokinetics; ADA= anti-drug antibodies

Note that PK samples for MK-3475 and anti-MK-3475-antibodies (ADA) will be collected from all patients in the study. Axitinib PK samples will be collected from all patients in the Dose Finding phase and at least 8 patients in the Dose Expansion Phase.

a. One sample (3 mL) collected at each time point for axitinib.
b. One sample (3 mL) collected at each time point for MK-3475. Additionally PK samples will be collected at 1 month, 3 months and 6 months after end of MK-3475 treatment.
c. One sample (6 mL) collected at each time point for MK-3475-antibodies.
d. Sample may be collected within 30 minutes after end of MK-3475 infusion.

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1. INTRODUCTION

1.1. Indication

Advanced RCC tumors in the first-line setting.

1.2. Background and Rationale

1.2.1. Renal Cell Cancer

An estimated 65,150 new cases of kidney cancer are expected to be diagnosed in the United States (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.[12]

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.[13] 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 tumorigenesis. Clear cell RCC is a highly vascular tumor with high expression of VEGF, VEGFRs and PDGF receptor.[14]

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.[15]

There are 7 molecularly 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), the monoclonal anti-VEGF antibody bevacizumab (given in combination with IFN alpha) 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.[15,16,17,18]

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Axitinib (INLYTA®, AG-013736)

Axitinib (INLYTA®, AG-013736) is an oral, small molecule, TKI selective for VEGFRs 1, 2 and 3 and is approved multinationally 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.[19] 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.

1.2.2.2. Clinical Safety and Efficacy of Axitinib

The safety and efficacy of axitinib were evaluated in a randomized, open-label, multicenter 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) for axitinib and sorfenib, respectively. 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, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.[9]

In a randomized, open-label, Phase 3 trial, treatment-naïve clear cell RCC patients were randomized (2:1) to receive axitinib (N=192) or sorafenib (N=96). There was no significant difference in median PFS between patients treated with axitinib or sorafenib 10.1 months (95% CI 7.2,12.1) vs 6.5 months (95% CI 4.7, 8.3), respectively, with stratified hazard ratio 0.77, (95% CI 0.56, 1.05). The axitinib ORR assessed by an Independent Review Committee was 32%, risk ratio 2.21, (95% CI 1.31, 3.75, stratified one sided p=0.0006). The most common adverse events (≥20%) observed with axitinib were diarrhea, hypertension, weight decrease, fatigue, decreased appetite, palmar-plantar erythrodysesthesia (hand-foot) syndrome, dysphonia, asthenia, hypothyroidism and nausea.[8]

Overall, the adverse events reported for axitinib in clinical studies were considered manageable and generally reversible. For single-agent axitinib, the most common adverse events (>20% of patients) reported from 699 cancer patients regardless of causality included diarrhea, fatigue, hypertension, decrease appetite, nausea, dysphonia, palmar-plantar erythrodysaesthesia syndrome, weight decreased, vomiting, constipation, headache, cough, arthralgia, dyspnea, and hemorrhagic events (including epistaxis, hematuria, hemoptysis, rectal hemorrhage, cerebral hemorrhage, gastric hemorrhage, and lower gastrointestinal hemorrhage). In addition, hypothyroidism and proteinuria were reported in 17.5% and 16.7% of the patients, respectively.

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the axitinib Investigator Brochure.[19]

1.2.2.3. Pembrolizumab(MK-3475)

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[25] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[26,27,28,29,30] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The Programmed Death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[31,32] The structure of murine PD-1 has been resolved.[33] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.[31,34,35,36] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[37,38] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[39,40] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[41] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[42,43,44,37] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation

triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[37] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma (MEL).[45] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab [Keytruda® (US); previously known as lambrolizumab, MK-3475 and SCH 9000475] is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was recently approved in the US for the treatment of advanced, unresectable or metastatic malignant melanoma, and for use in melanoma patients with disease progression after prior treatment with (a) ipilimumab or (b) a BRAF inhibitor, in the case of BRAF V600-mutant disease.[50]

1.2.2.4. Clinical Safety and Efficacy of MK-3475

The safety of MK-3475 is being assessed in six ongoing clinical trials, PN001, PN002, PN006, PN010, PN011 and PN012. Safety data of single-agent MK-3475 are only available from Study PN001 at this time. Protocol 001 (PN001) is an open-label Phase 1 study, which includes a dose-escalation component in patients with solid tumors (Part A) and with subsequent expansion cohorts in patients with melanoma (Parts B and D) and NSCLC (Parts C and F). PN001 Part A evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered Q2W. All three dose levels were well tolerated and no dose-limiting toxicities were observed. Based on PK data showing a half-life of 21 days, the protocol was amended to include a dosing frequency of Q3W in the expansion cohorts (Parts B through F).

Preliminary data (as of 26 July 2013) are available from 479 patients enrolled in PN001: Part A (n=30) 1 mg/kg, 3 mg/kg, and 10 mg/kg MK-3475 dosed Q2W to Q3W, Part B (n=308) 2 mg/kg or 10 mg/kg MK-3475 dosed Q2W to Q3W, Part C (n=38) 10 mg/kg MK-3475 dosed Q3W, and Part D (n=103) 2 or 10 mg/kg MK-3475 dosed Q3W. Of the 479 patients who have received MK-3475 in Protocol 001, 466 (97.3%) experienced treatment emergent adverse events (AEs) of which 368 (76.8%) were considered drug-related. Serious adverse events (SAEs) were reported in 30.1% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by Investigators were reported in 6.7% of patients overall. Potentially immune-related AEs have been observed, including pneumonitis (Grade 1-2) in both melanoma and NSCLC cohorts. The most commonly reported treatment emergent AEs experienced are fatigue, nausea, cough, pruritus, diarrhea and rash. Most patients continued treatment in spite of adverse events, and only 4.2% of patients discontinued study treatment due to an AE that was considered related to study treatment by Investigators.

Of the 162 patients who received 2 mg/kg MK-3475 dosed Q3W (Parts B1, B2 and D) in PN001, 160 (98.8%) experienced treatment emergent AEs of which 128 (79.0%) were considered to be drug-related. SAEs were reported in 27.2% of patients, but SAEs that were attributed as potentially (possibly, probably, or definitely) drug-related by Investigators were reported in 9.3% of this subset of patients. The most commonly reported treatment emergent AEs experienced in this subset up patients are fatigue, nausea, cough, pruritus, rash and diarrhea.

Thus, the overall AE summary suggests that MK-3475 is generally tolerable and AEs are generally manageable in patients.

The SRSD for combination agent MK-3475 is the MK-3475 Investigator Brochure.[20]

1.2.3. Rationale for Studying Axitinib in Combination with MK-3475 in Patients with Advanced Renal Cell Carcinoma

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 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 pathway 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 aRCC.[10,11]

There is a strong rationale for considering immunotherapy in RCC patients. Cytokine based immunotherapy, especially high dose of IL-2, exhibited durable response in some aRCC patients. There are anecdotal reports of spontaneous remissions in aRCC patients with evidence of antigen-specific lymphocyte infiltration of tumor tissues.[2] These evidences have generated considerable interests in immunotherapeutic approaches in the treatment of aRCC patients, especially with advent of immune-check point inhibitors such as anti-PD1 and anti PD L1 antibodies in recent years. Upregulations of programmed death-1 (PD-1) receptor on tumor-infiltrating lymphocytes, and its ligand PD-L1 on tumors are associated with more aggressive disease and poor prognosis.[3,4]

Blocking the PD-1/PD-L1 interaction in aRCC is a novel immunotherapeutic approach, which has shown single agent efficacy in patients whose disease have progressed following VEGF pathway inhibitor therapy.[6,7] BMS-936558, also named nivolumab, is a fully humanized anti-PD-1 antibody (Bristol-Myers Squibb) that has shown anti-tumor activity in 296 patients with solid cancers.[5] Among these 296 patients, 33 patients had aRCC and were heavily pretreated before nivolumab therapy. Nivolumab was given at a starting dose of 1 mg/kg and then expanded to 10 mg/kg. The objective response rate (ORR) was 27% (9/33) and another 9 patients (27%) had stable disease at the 24-week follow-up. Five patients had durable response longer than 1 year.[5] It is therefore proposed that combining a PD-1

inhibitor with a VEGF pathway inhibitor may provide clinical benefit compared to treatment with a VEGF pathway directed therapy alone.[5]

Antitumor activity of single agent axitinib in treatment-naïve patients with clear cell RCC was assessed against sorafenib in a randomized, open-label, phase 3 trial. Although the study did not demonstrate statistically significant difference in median PFS between patients treated with axitinib or sorafenib, axitinib was associated with a longer mPFS value {median PFS of 10.1 months (95% CI 7.2,12.1) with axitinib vs. 6.5 months (95% CI 4.7, 8.3) with sorafenib, stratified hazard ratio 0.77, (95% CI 0.56, 1.05)}. The median PFS observed with axitinib in this study was similar to those demonstrated earlier in phase 3 clinical trials with other approved VEGF TKIs in treatment-naïve aRCC patients.[8] Toxicities in this clinical trial were manageable and similar to the clinical trials with axitinib done in pre-treated aRCC patients.[9]

It is therefore proposed that combining MK-3475 with axitinib may provide clinical benefit in treatment-naïve aRCC patients compared to treatment with a VEGF pathway directed therapy alone.

After the collection of data to verify the primary study objective and most of the secondary objectives of the study has been completed, this study (A4061079) will remain open to give patients an opportunity to continue to receive study treatment as described in Section 3 of this protocol. Guidance on the management of patients who continue on study (ie, patients who are still clinically benefiting from study treatment without unacceptable toxicity or disease progression and who have not withdrawn consent) is provided to investigators in Appendix 6. Clinical assessments will be reduced in scope and the required schedule of activities will be revised to maintain only those assessments that protect the well-being of the patient.

1.2.4. Rationale for Axitinib and MK-3475 Starting Doses in This Trial

1.2.4.1. Axitinib Starting Dose

In this trial, the axitinib starting dose will be 5 mg BID with or without food. This dose has proven to be safe and efficacious in RCC and has been approved by regulatory authorities worldwide.

1.2.4.2. MK-3475 Starting Dose and Regimen

In this trial, the MK-3475 starting dose will be 2 mg/kg to be administered every 3 weeks (Q3W), based on the following observations:

- The MK-3475 Phase 1 dose escalation study in patients with solid tumors showed that MK-3475 was safe at the tested dose levels (1 mg/kg, 2 mg/kg and 10 mg/kg, administered every 2 weeks) without reaching a maximum tolerated dose. In addition, clinical responses were observed at all the dose levels.[21]

- The dose of 2 mg/kg dosed Q3W was well tolerated based on published[21] single agent safety and tolerability data from the Phase 1 first-in-human study (PN001). In this study, MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). PK data analysis of MK-3475 administered in Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life, typical for therapeutic antibodies (refer to MK-3475 IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing either Q2W or Q3W dosing schedules.

- In the ongoing PN001 protocol, patients with ipilimumab-naïve or ipilimumab-pretreated advanced melanoma were treated on three different dosing regimens of MK-3475: 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. An interim analysis has suggested that there are no major differences in the safety profile or overall objective response rate for the doses of 2 mg/kg or 10 mg/kg given Q3W.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To assess the safety and tolerability of axitinib in combination with MK-3475 in patients with previously untreated advanced RCC in order to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D).

Secondary Objectives

- To evaluate the overall safety profile of axitinib in combination with MK-3475.

- To assess the anti-tumor activity of axitinib in combination with MK-3475 in patients with advanced RCC in the first-line treatment setting.

- To characterize the pharmacokinetics (PK) of axitinib and axitinib plus MK-3475 when administered in combination and to assess the effect of MK-3475 on the PK of axitinib.

- To characterize, using translational approaches, genes and proteins such as PD-L1, VEGF-A and IL-8 relevant to angiogenesis drug target pathway, renal cell carcinoma biology, and sensitivity/resistance mechanisms to axitinib in combination with MK-3475 in tumor and/or blood.

- To explore the pharmacodynamic effect of axitinib in combination with MK-3475 in blood and tumor by assessment of gene, RNAs and proteins including but not limited to VEGF-A, IL-8, VEGFR2 and T-cell receptors.

- To assess the immunogenicity of MK-3475.

2.2. Endpoints

Primary Endpoint

- First 2 cycles (6 weeks) DLTs.

Secondary Endpoints

- Adverse events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI 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]).
- Objective tumor response, as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.
- Time-to-event endpoints (Dose Expansion Phase): Duration of Response (DR) and Progression-Free Survival (PFS) and Overall Survival (OS).
- PK parameters of axitinib and MK-3475: C_{max}, T_{max}, AUC_{0-12}, CL/F and V/F as data permit for axitinib and population-based PK parameters for MK-3475.
- Immunogenicity (anti-drug antibodies; ADA) of MK-3475.
- Biomarkers including but not limited to PD-L1 and VEGF-A in tumor biospecimens.
- Pre- and post-dose serum biomarkers (including but not limited to VEGF-A, VEGFR2 and IL-8) and whole blood biomarkers (including but not limited to T cell receptor status).

3. STUDY DESIGN

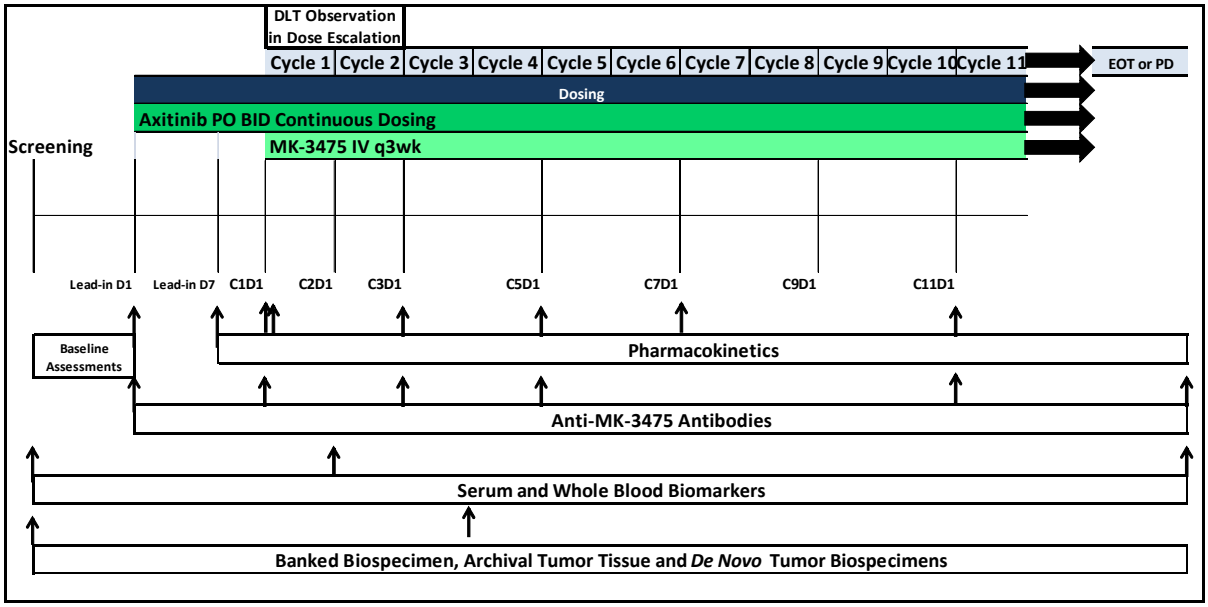
3.1. Study Overview

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of axitinib in combination with MK-3475 in adult patients with previously untreated advanced RCC. This clinical study will be composed of a Dose Finding Phase and a Dose Expansion Phase. The Dose Finding Phase will estimate the MTD in patients with advanced RCC patients with clear cell histology who did not receive any prior systemic therapy for their advanced disease, using the modified toxicity probability interval (mTPI) method.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for axitinib in combination with MK-3475 in patients with advanced RCC who did not receive prior systemic therapy. The Expansion Test Dose will be either the MTD (ie, the highest dose of axitinib and MK-3475 associated with the occurrence of DLTs in <33% of patients) or the RP2D, 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 MK-3475 will be tested in patients with previously untreated advanced RCC.

Approximately 60 patients (including Dose Finding Phase and Dose Expansion Phase) are expected to be enrolled in the study.

Figure 1. Study Schema



Study Treatment: Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule. MK-3475 will be given as 30-minute intravenous infusion every 3-weeks. In all patients, treatment with study drugs will continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, whichever occurs first, or the study is terminated by the Sponsor (see Section 6.4 Study Withdrawal).

Patients will be monitored closely for toxicity and in the event of significant toxicity dosing may be delayed and/or reduced (Section 5.2.7). Axitinib and MK-3475 dose modifications for drug-related toxicities are described in the Table 5 and Table 6. Based on the known safety profile of axitinib, blood pressure as well as thyroid function will be monitored throughout the treatment period. Axitinib treatment may be adjusted by dosing interruption with or without dose reduction (Section 5.2.7.2). Based on data emerging from trials of VEGF tyrosine kinase inhibitors given in combination with PD-1 inhibitors, liver function tests will be monitored closely for the first 3 cycles.[49] MK-3475 dose modification and

supportive care for drug related toxicities, including immune-related adverse events (irAEs are described in Section 5.2.7.4.

Intra-patient dose escalation for axitinib is permitted only after completing 12 weeks of treatment if the starting dose of axitinib is 5 mg BID (DL1), and after 6 weeks if axitinib starting dose is 3 mg BID (DL-1) (Section 5.2.7).

The treatment duration with MK-3475 is 24 months calculated from the date of the first dose of MK-3475. Continuation of treatment with MK-3475 beyond 24 months should be discussed with the sponsor and not go beyond 36 months. After completing treatment with MK-3475, patients experiencing objective response or stable disease may continue on treatment with axitinib single agent until disease progression, patient refusal, unacceptable toxicity or the study is prematurely terminated by the Sponsor; whichever comes first (please see Section 6.4, Patient Withdrawal).

Discontinuation from MK-3475 may be considered at the investigator's discretion for patients who have attained a confirmed CR, have received at least 24 weeks of treatment with MK-3475, and have received at least two MK-3475 infusions beyond the date the CR was initially declared. Axitinib may be continued in those patients. Patients who then experience radiologic disease progression will be eligible for re-treatment with MK-3475 at the discretion of the investigator if no other cancer treatment was administered other than axitinib since the last dose of MK-3475, the patient still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is still open. Patients will resume MK-3475 therapy at the same dose and schedule in place at the time of discontinuation. MK-3475 treatment will be administered for up to one additional year.

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).

Tumor assessment: Anti-tumor activity will be assessed by radiological tumor assessments conducted at baseline, then at 12 weeks and every 6 weeks thereafter, using RECIST version 1.1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions according to RECIST v 1.1 (see Study Reference Manual).

If radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD. Assigned study treatment may be continued at the investigator's discretion while awaiting radiologic confirmation of progression. If repeat imaging does not confirm PD, study treatment may be continued/resumed. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD and can discontinue treatment immediately.

If the repeat imaging confirms PD (Section 5.2.4.1) patients may be discontinued from treatment. However, according to the investigator's clinical judgment and after discussion between the investigator and the Sponsor, if a patient with evidence of disease progression is still experiencing clinical benefit, he/she will be eligible for continued treatment with single agent axitinib, MK-3475 or axitinib combined with MK-3475 as long as the following criteria are met:

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

Brain CT or MRI scans are required at baseline and when there is a suspected brain metastasis. Bone scans: Bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT is required at baseline then every 12 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.

Retrospective central review of all imaging time points may be performed for this study, therefore all imaging source data should be retained at the site and be available for future inspection or further analysis. Additional information is included in the Study Reference Manual.

Pharmacokinetic assessment: MK-3475 and axitinib do not have competing elimination/metabolism pathways, hence an overt PK interaction between the two drugs is not anticipated. However, pharmacokinetic assessments will be conducted in this study to confirm the absence of drug-drug interactions. To understand the PK effects of MK-3475 on axitinib, a 7-day lead-in period of single-agent axitinib will be included prior to Cycle 1 in all patients in the Dose Finding Phase and in at least 8 patients in the Dose Expansion Phase of the study. Axitinib has a plasma half life of 2.5-4.1 hours and is expected to reach steady-state within 2 to 3 days of dosing. MK-3475 has a long plasma half-life (21-28 days) and trough concentrations increase with successive doses until steady state, which is expected within 5 months of MK-3475 dosing. The administration of single agent MK-3475 to this patient population is not considered in this trial. Therefore, the effect of axitinib on MK-3475 will be evaluated by comparing MK-3475 pharmacokinetics at steady-state in the presence of axitinib with those reported for MK-3475 alone in prior studies. At least 8 patients (target is 8 PK evaluable patients) from the Dose Expansion Phase will participate in PK assessments, therefore these patients will undergo the 7-day lead-in period for axitinib. There will be no lead-in period for the remaining patients in the Dose Expansion Phase.

Tumor biopsy assessment and translational studies: Archived (all patients) and baseline *de novo* tumor biospecimens from metastatic lesions (Dose Expansion Phase only) will be collected for retrospective assessment. For all patients in the Dose Expansion Phase, a second tumor biopsy is strongly encouraged at the time of first tumor assessment (ie, 12 weeks) to assess the effects of the combination on the relevant pathways. Biomarker studies on tumor biospecimens including but not limited to tumor PD-L1 expression and blood levels of VEGF-A, IL-8 and VEGFR-2, will be carried out to help understand the mechanism of action of the axitinib plus MK-3475 combination, pharmacodynamic effects, as well as potential mechanisms of sensitivity and resistance. Such results may help in the future development of this combination. Analyses using translational approaches may also result in the identification of potential biomarkers of response to the axitinib plus MK-3475 combination, ultimately leading to development of a patient selection strategy for further clinical investigation. As such collection of tumor tissue and blood specimens at baseline and on study will be of paramount importance.

3.1.1. Dose Finding Phase

3.1.1.1. Starting Doses for Axitinib and MK-3475 (Dose Level 1)

The starting doses (Dose Level 1) are axitinib 5 mg BID and MK-3475 2 mg/Kg IV Q3W in three-week cycles.

3.1.1.2. Criteria for Dose Finding

Dose finding will follow an "Up-and-Down" design, using doses of MK-3475 and axitinib as shown in Table 1.

Table 1. Dose Levels in the Dose Finding Phase

Dose Level	MK-3475	Axitinib
1 (Starting Dose Level)	2 mg /kg IV q3wk	5 mg BID
-1	2 mg /kg IV q3wk	3 mg BID

BID: twice daily; q3wk: every 3 weeks

Possible dose finding scenarios based on the starting (1) dose level tolerability are illustrated in Table 2. DL-1 will be explored only if the MTD is exceeded already at DL1.

In this dosing algorithm there are up to 2 potential dose levels (DL): (DL-1) MK-3475 2 mg/kg q3wk + axitinib 3 mg BID and (DL1) MK-3475 2 mg/kg q3wk + axitinib 5 mg BID.

Alternative doses, schedule(s) and PK time points may be reconsidered during the study based on the emerging safety and PK data.

There are several potential dosing finding sequences for MK-3475 + 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

Possible sequences starting at Dose Level 1
DL1
DL1 → DL-1
DL1 → DL-1→ DL1

Dosing will begin at DL1 and possibly de-escalated to DL -1 according to Table 3. Dose escalation from DL -1 back to DL 1 will be allowed as long as DL 1 has not been determined to have exceeded the MTD. The escalation/de-escalation rules will follow the mTPI method[23] (see Section 9.2). 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. The detailed dose-finding rules based on the mTPI are illustrated in Table 3.

Table 3. Detailed Dose Escalation/De-Escalation Scheme

		Number of patients treated at current dose									
		1	2	3	4	5	6	7	8	9	10
Number of toxicities	0	NA	NA	E	E	E	E	E	E	E	E
	1	NA	NA	S	S	S	E	E	E	E	E
	2		NA	D	S	S	S	S	S	S	S
	3			DU	DU	D	D	S	S	S	S
	4				DU	DU	DU	DU	DU	DU	DU
	5					DU	DU	DU	DU	DU	DU
	6						DU	DU	DU	DU	DU
	7							DU	DU	DU	DU
	8								DU	DU	DU
	9									DU	DU
	10										DU

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
NA = Not Applicable. The first three patients will have to be evaluable for DLT before assigning DL for the next patient
MTD = 30%

As an example, if the total number of patients treated at DL1 is 3 the following dosing rules are applied:

- 0 - 1 DLT → remain at the same dose (DL1);
- 2 DLTs → de-escalate to DL-1 and allow for possible escalation back to DL1;

- 3 DLTs → de-escalate to DL-1 and consider DL1 as intolerable.

If the dose is de-escalated to DL-1 and the total number of patients then treated at DL-1 is 3 the following dosing rules are applied:

- 0 DLTs → escalate back to DL1;
- 1 DLT → remain at the same dose (DL-1);
- 2-3 DLTs → de-escalation not possible consider DL-1 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 at each dose level will initiate dosing sequentially, at least 2 days apart from each other to allow for the initial evaluation of toxicities and tolerability. If the first 2 patients experience a DLT prior to enrollment of the third one, the dose level will be deemed intolerable and the dose level will be de-escalated. 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 6 weeks (ie, the first 2 treatment cycles), or experience a DLT, whichever comes first.
- If a patient withdraws from study treatment before receiving at least 75% of the planned first two cycles dose of axitinib or two infusions of MK-3475 within the DLT observation period for reasons other than study drug-related toxicity, another patient will be enrolled to replace that patient at the current dose level.
- The dose-finding component of the trial is completed when 10 DLT-evaluable patients have been treated at the highest dose associated with DLT rate <0.33. It is estimated that approximately 20 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 determination from the Dose Finding Phase, and other factors related to safety, efficacy, and PK/PD involving all available data from test cohorts.

No intrapatient dose escalation will be permitted in the Dose Finding Phase.

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 Finding, any of the following adverse events occurring during the DLT observation period (6 weeks) that are attributable to one or both study drugs 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 non-laboratory toxicities despite maximum supportive therapy.

  Grade ≥3 hypertension despite maximal medical therapy.

- Non-hematologic Grade ≥3 laboratory value if:

  Medical intervention is required to treat the patient, or

  The abnormality leads to hospitalization.

- Inability to complete at least 75% of axitinib dosing or two infusions of MK-3475 within the 6-weeks DLT observation period due to treatment-related toxicity.

3.2. Maximum Tolerated Dose Definition

The MTD estimate is the highest dose of axitinib and MK-3475 associated with the occurrence of DLTs in <33% of patients.

3.3. Dose Expansion Phase Test Dose Definition

The Expansion Test Dose will be the MTD identified in the Dose Escalation Phase. Further experience in the Dose Expansion Phase cohort may result in the need to explore a lower Expansion Test Dose.

3.3.1. Dose Expansion Phase

All patients in the Dose Expansion Phase may be enrolled simultaneously.

3.4. Recommended Phase 2 Dose Definition

The RP2D is the dose of axitinib and MK-3475 in combination chosen for further clinical development. If the MTD proves to be clinically feasible for long term administration in a reasonable number of patients, this dose usually becomes the RP2D. Further experience in the Dose Expansion Cohort may result in a RP2D dose lower than the MTD.

For axitinib, intra-patient dose escalation to higher doses may be permitted after 12 weeks of treatment if the starting dose of axitinib is 5 mg BID (DL1), and after 6 weeks if axitinib starting dose is 3 mg BID (DL-1) (see Section 5.2.7.1).

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 protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

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

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

1. Diagnosis

    - Histologically or cytologically confirmed advanced RCC with predominantly clear cell subtype.
    - Primary tumor resected.
    - Mandatory archival tumor biospecimen (all patients) and baseline de novo biopsy from a metastatic lesion (Expansion Cohort only). Formalin fixed, paraffin embedded [FFPE] tissue block(s) or at least 12 unbaked, unstained slides are required. Tissue samples taken from a metastatic lesion prior to the start of screening are acceptable.
    - 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. No evidence of pre-existing 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.

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

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

11. 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).

12. Male and female patients of childbearing potential must agree to use two highly effective methods of contraception throughout the study and for at least 120 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 systemic therapy directed at advanced RCC.

2. Prior adjuvant or neoadjuvant therapy if disease progression or relapse has occurred during or within 12 months after the last dose of treatment.

3. Prior therapy with axitinib (AG-013736).

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

5. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study entry.

6. Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be an exception. Patients that require intermittent use of bronchodilators or local steroid injections and patients with hypothyroidism stable with hormone replacement will not be excluded from study.

7. Major surgery <4 weeks or radiation therapy <2 weeks of study entry. Prior palliative radiotherapy (≤10 fractions) to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to the initiation of study medication and there is at least one measurable lesion that has not been irradiated.

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

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

10. Evidence of inadequate wound healing.

11. Active bleeding disorder or other history of significant bleeding episodes within 30 days before study entry.

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

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

14. Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

15. Deep vein thrombosis or pulmonary embolism within 6 months prior to study drugs administration.

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

17. Active infection requiring systemic therapy.

18. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

19. Administration of a live vaccine within 30 days prior to the first dose of trial treatment.

20. 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.

21. Current use or anticipated need for treatment with drugs or foods that are known 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. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

22. Current use of anticipated need for treatment with drugs that are known strong CYP3A4/5 inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort.

23. 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 or low grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation or castration).

24. 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.

25. Participation in other studies within 4 weeks before the current study begins and/or during study participation.

26. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for *at least 120 days* after last dose of study drugs.

27. 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.

4.3. Life Style Guidelines

4.3.1. Contraception

In this study, fertile male patients and female patients who are of childbearing potential will receive axitinib, which has been associated with teratogenic risk, in combination with MK-3475. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and continued for at least 120 days after the last dose. The Investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the Investigator or designee will instruct the patient to call immediately if 1 or both of the

selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

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

- Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner 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.

- Correctly placed copper containing intrauterine device (IUD).

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

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

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

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 Study Reference 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 Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are axitinib and MK-3475.

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 study drug 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. Drug Supplies

Axitinib (AG-013736) and MK-3475 will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment & Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment & Proof of Receipt form. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.2.1. Formulation and Packaging

5.2.1.1. Axitinib

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

5.2.1.2. MK-3475

MK-3475 will be supplied in single-use vials containing 100 mg/4mL sterile solution for intravenous administration. Each vial is sealed with a coated stopper and oversealed and labeled according to local regulatory requirements.

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 will be provided in quantities appropriate for the study visit schedule. A qualified staff member will provide the study medication via a unique container number using the drug management system.

Axitinib will be dispensed every 3 weeks 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.

MK-3475 will be dosed at the investigational site as indicated in Section 5.2.4.1.

Specific preparation and dispensing instructions are provided in the Dosage Administration Instruction located in the Study Manual.

5.2.3. Administration

All trial treatment will be administered on an outpatient basis.

5.2.3.1. Axitinib

Axitinib will be 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 5.2.7.2). Axitinib tablets are to be taken approximately 12 hours apart and may be administered without regard to meals. Tablets must not be crushed, split or dissolved and patients should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing.

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 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 (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.

Treatment with axitinib will continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, whichever occurs first, or the study is terminated by the Sponsor (see Section 6.4, Patient Withdrawal).

5.2.4. MK-3475

5.2.4.1. MK-3475 Timing of Dose Administration

MK-3475 will be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Schedule of Activities table. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

MK-3475 will be administered as a 30 minute IV infusion every 3-weeks, next cycle administration may be delayed due to persisting toxicity as described in Section 5.2.7.

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

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). The exact duration of infusion should be recorded in both sources document and CRFs.

The dose amount required to prepare the MK-3475 infusion solution will be based on the patient's weight in kilograms (kg).

For purposes of this trial, an overdose will be defined as any dose ≥20% over the prescribed dose for the standard treatments. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If a dose of MK-3475 meeting the protocol definition of overdose is administered without inducing any associated clinical symptoms or abnormal laboratory results, then the overdose is reported in CRF as a non-serious adverse event, using the terminology "accidental or intentional overdose without adverse effect." Also see Section 5.2.5 Medication Errors.

The Study Reference Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.4.2. MK-3475 Treatment Duration

The treatment duration with MK-3475 is 24 months calculated from the date of the first dose of MK-3475. Continuation of treatment with MK-3475 beyond 24 months should be discussed with the sponsor and should not go beyond 36 months. Patients who stop MK-3475 for reasons other than confirmed disease progression may continue on treatment with axitinib single agent until disease progression (RECIST v. 1.1), patient refusal, and unacceptable toxicity occurs; or the study is prematurely terminated by the Sponsor; whichever comes first (see Section 6.4 Patient Withdrawal).

Discontinuation from MK-3475 treatment may be considered at the investigator's discretion for patients who have attained a confirmed CR, that have been treated for at least 24 weeks with MK-3475 and have at least two treatments with MK-3475 beyond the date the initial CR was declared. Axitinib treatment may continue in these patients. Patients who then experience radiologic disease progression will be eligible for treatment (see Section 5.2.4.2.1) with MK-3475 at the discretion of the investigator if no cancer treatment was administered other than study drugs since the last dose of MK-3475, the patient meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial is open. Patients will resume therapy at the same dose and schedule at the time of initial discontinuation. MK-3475 treatment will be administered for up to one additional year.

5.2.4.2.1. Treatment after Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as MK-3475 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD. Study treatment may continue according to the investigator's discretion while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden demonstrating CR, PR or SD compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Study Reference Manual).

If the repeat imaging demonstrates confirmed evidence of PD, progressive disease, patients may be discontinued from the study. However, according to the investigator's clinical judgment and after discussion between the investigator and the Sponsor, if a patient with evidence of disease progression is still experiencing clinical benefit, the patient will be eligible for continued treatment with single agent axitinib, MK-3475 or axitinib combined with MK-3475. The investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

5.2.5. 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 (refer to ADVERSE EVENT REPORTING section for further details).

5.2.6. Food Requirements

Axitinib can be taken with or without food. MK-3475 is administered as a 30-minute intravenous infusion without regard to food.

5.2.7. Recommended Dose Modifications

Every effort should be made to administer study treatment 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 three ways:

- Within a cycle (for axitinib only): dosing interruption until adequate recovery, if required, during a given treatment cycle.
- Between cycles (for MK-3475 only): next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start
- In the next cycle (for axitinib only): 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.

Dose modifications will be reported in the CRF.

Axitinib dose levels for intrapatient dose modification are listed in Table 4.

5.2.7.1. Axitinib Intra-Patient Dose Increase

Axitinib intra-patient dose increase is permitted only after completing 12 weeks of axitinib treatment if the starting dose of axitinib is 5 mg BID (DL1), and after 6 weeks if axitinib starting dose is 3 mg BID (DL-1) Table 1.

Patients who tolerate the current axitinib dose with no grade >2 drug-related 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 4, 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). Particular attention should be provided to a patient's overall safety profile prior to implementing intra-patient dose increase for axitinib.

Table 4. Axitinib Dose Levels

Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
Starting dose	5 mg BID
-1	3 mg BID
-2	2 mg BID

5.2.7.2. Axitinib Dose Modifications in Case of Drug-Related Toxicity

Patients will be monitored closely for toxicity, and axitinib treatment may be adjusted by dosing interruption with or without dose reduction as indicated below. Dose modification can occur independently for the 2 drugs used in this study. Dosing interruption and/or 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 level (2 mg BID), axitinib should be permanently discontinued. Management of patients requiring more than 2 dose reductions should be discussed with the Sponsor.

5.2.7.3. 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 axitinib 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 (see Section 5.4).[47,48]

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

Table 5. Axitinib Dose Modifications for Drug-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification
Hematologic Laboratory Abnormalities	Grade 1, 2 or 3	Continue at the same dose level.
	Grade 4	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.
AST, ALT with total bilirubin <2xULN and PT/INR <1.5xULN	Grade 1	Continue at the same dose level
	Grade 2	Withhold until resolution to <2xULN or baseline. Restart at same dose level or one lower dose level.
	Grade 3 and 4	Withhold until resolution to <2xULN or baseline. Restart at one lower dose level.
AST/ALT Elevation with clinically significant hepatic dysfunction (ie, total bilirubin ≥2xULN excluding biliary obstruction or PT/INR ≥1.5xULN)		***Permanently discontinue*** and follow-up per protocol.
Non-hematologic Toxicities, Laboratory Abnormalities and/or Other Drug Related Toxicities[b]	Grade 1	Continue at the same dose level.
	Grade 2	Continue at the same dose level.
	Grade 3	Reduce by 1 dose level. Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than LFTs) laboratory abnormalities may continue at the same dose level per Investigator judgment.
	Grade 4	Other non-hematologic/laboratory and non-laboratory abnormalities, hold treatment until recovery to Grade <2 then, reduce by 1 dose level and resume treatment. Grade 4 asymptomatic biochemistry laboratory (other than LFTs) abnormality: study treatment may continue without interruption per Investigator's judgment.
Proteinuria	Dipstick negative or shows 1+ (Grade 1)	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	Continue at the same dose level.

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification
	≥2 g proteinuria/ 24 hours	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 judgment.
Hypertension	2 systolic BP readings separated by at least 1 hour show systolic pressure ≤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)	Continue at the same dose level See Section 5.2.7.3 for monitoring/management of axitinib-related hypertension
	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	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 5.2.7.3 for monitoring/management of axitinib-related hypertension.
	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	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 5.2.7.3 for monitoring/management of axitinib-related hypertension
	Recurrent hypertension following previous dose reduction (2 systolic BP readings separated by at least 1 hour show 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	Repeat dose reduction by one lower dose level. See Section 5.2.7.3 for monitoring/management of axitinib-related hypertension.
Hypophysitis	Grade 1	Continue at the same dose level.
	Grade 2-4	Continue at the same dose level.

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification
Type 1 diabetes mellitus (if new onset) or hyperglycemia	Grade 1-2	Continue at the same dose level.
	Grade 3-4	Continue at the same dose level or follow guidelines in non-hematologic toxicities.
Diarrhea/Colitis	Grade 1	Continue at the same does level.
	Grade 2	Continue at the same dose level.
	Grade 3	Reduce by 1 dose level. Follow the guidelines as in non-hematologic toxicities in Table 5.
	Grade 4	Follow the guidelines as in non-hematologic toxicities in Table 5.
Pneumonitis	Grade 1	Continue at the same dose level.
	Grade 2	Continue at the same dose level or follow the guidelines in non-hematologic toxicities.
	Grade 3-4	Follow the guidelines in non-hematologic toxicities.
Hyperthyroidism	Grades 1-2	Continue at the same dose level.
	Grade 3	Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry (other than LFTs) laboratory abnormalities: may continue at the same dose level or reduce by one dose level per Investigator judgment.
	Grade 4	Interrupt until recovery to Grade <2 then reduce by one lower dose level
Renal Failure or Nephritis	Grade 1	Continue at the same dose level
	Grade 2	Continue at the Same dose level
	Grade 3 and 4	Hold treatment until recovery to Grade ≤2. Then, reduce by 1 dose level and resume treatment.

5.2.7.4. MK-3475 Immune-Related Adverse Events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6. Additional guidance can be found in the Pembrolizumab Events of Clinical Interest Guidance Document.

Table 6. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
				to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

5.2.8. 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 axitinib compliance. The diary will be maintained by the patient to include missed or changed axitinib doses.

Patients will be required to return all bottles of axitinib after every cycle (every 21 days). The number of axitinib tablets remaining will be documented and recorded at each clinic visit. The patient diary may also be used to support this part of the axitinib accountability process.

The site is to follow up (for example, via a telephone call) with each patient at Cycle 1 Day 5 (+2 days) to confirm that the patient understands and is in compliance with axitinib dosing instructions. If needed, the patient will be re-trained. The same follow up process will be applied in case the dose of axitinib is modified during the treatment period.

5.3. Drug Storage and Drug Accountability

The Investigator, or an approved representative (eg, pharmacist), will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

- Axitinib must be stored at controlled room temperature (between 15-30°C) or as specified on the label.

- MK-3475 must be stored under storage conditions specified on the label.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

Specific details regarding information the site should report for each excursion will be provided to the site. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions. Site staff will instruct patients on the proper storage requirements for take home investigational products.

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. 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. The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.4. Concomitant Medication(s)

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

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 MK-3475 is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.4.1. Inhibitors and Inducers of CYP Enzymes (Axitinib)

In vitro studies with human liver microsomes and recombinant CYP enzymes indicate that axitinib metabolism is primarily mediated by the CYP3A4/5, and to a lesser extent by CYP1A2, CYP2C19 and UGT1A1.

The concomitant use of strong CYP3A4/5 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although axitinib dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of axitinib by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be modified based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the axitinib dose should be returned (after 3 – 5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Co-administration of axitinib with strong CYP3A4/5 inducers (eg, rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended. Moderate CYP3A4/5 inducers (eg, bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

5.4.2. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first 6 weeks of treatment but they may be used to treat treatment emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[45]

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.

5.4.3. Concomitant Surgery

5.4.3.1. Axitinib

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, provided that wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

5.4.3.2. MK-3475

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy such as elective surgery, unrelated medical events, patient vacation and holidays. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for the interruption should be documented.

5.4.4. Concomitant Radiotherapy

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

5.4.5. Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

5.4.6. Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than axitinib and MK-3475.
- Radiation therapy.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.

Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of therapeutic doses of corticosteroids may be approved for symptomatic treatment after consultation with the Sponsor.

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

5.5. Rescue Medications & Supportive Care

5.5.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- 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 dose heparin cannot be administered, the administration of coumadin or other coumarin derivatives or other anti-coagulants may be allowed; however appropriate monitoring of prothrombin time/International normalized ratio (PT/INR) should be performed.

5.5.2. Management of MK-3475 Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 7 below shows treatment guidelines for patients who experience an infusion reaction associated with administration of MK-3475.

Table 7. MK-3475 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAID, narcotics, IV fluids); prophylactic medications indicated for < = 24 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluid Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patients is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Patients may be premedicated 1.5 hour (±30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3; Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor of ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine** Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Patient is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6. STUDY PROCEDURES

6.1. Screening

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

6.1.1. Tumor Biospecimens

Provision of archival tumor biospecimens (all patients) and baseline *de novo* biospecimens from metastatic lesions (expansion cohort) is mandatory for all patients. Although baseline *de novo* biopsies taken from metastatic lesions prior to the date of screening are acceptable, sponsor provided neutral buffered formalin in kits for preferred collection on the date of screening to optimize tissue fixation for subsequent analysis. A second *de novo* biopsy is strongly encouraged and collected at the time of first tumor assessment at after 4 Cycles of treatment (12 weeks). It is recommended, if possible, that the 12 week biopsy be taken from a lesion in the same anatomical location and also fixed in sponsor provided neutral buffered formalin.

For archival tumor biospecimens, formalin fixed, paraffin embedded (FFPE) tissue block(s) from initial diagnosis that contain sufficient tissue to generate at least 12 slides, each with tissue sections (4 microns thickness preferred, 5 microns thick acceptable), will be collected. If no FFPE block is available, then at least 12 unbaked and unstained slides containing FFPE tissue sections, 5 microns thick acceptable). However FFPE blocks are strongly encouraged over slides. See Section 7.3.1. Additional information on tumor biospecimen collection, processing and immediate shipping procedures is included in the study laboratory manual.

6.2. Study Period

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

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

For follow-up procedures see Schedule of Activities (SOA) and ASSESSMENTS section (Section 7). All patients should be followed for survival at least every 3 months after discontinuing study treatment. Survival monitoring will continue until 3 years after Cycle 1 Day 1 of the last patient enrolled in the study.

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 (see also the Withdrawal From the Study Due to Adverse Events and the Patient Withdrawal section) 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 investigator site.

Reasons for discontinuation of study treatment may include:

- Confirmed 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, MK-3475 or axitinib plus MK-3475 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;
- Refused 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 return all unused investigational product(s), request the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

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.

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

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.

For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

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 therapy - once at the start of screening and once at the baseline visit, immediately before starting the investigational products. Following a negative pregnancy result at screening, appropriate contraception must be commenced and a further negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational products. Pregnancy tests will be repeated at every treatment cycle during the active treatment period, at the end of study treatment and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, 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.

7.1.2.1. MK-3475 Adverse Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms and reported within 24 hours to the Sponsor. Sponsor Contact information can be found in the Study Reference Manual.

ECIs for this trial include:

1. An overdose of Sponsor's product, as defined in Section 5.2.4.1. MK-3475 Timing of Dose Administration that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Study Reference Manual.

3. Additional adverse events

A separate guidance document has been provided entitled “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document can be found in the Study Reference Manual and provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event.

Patients should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an immunerelated event. Patients who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur to any patient from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Study Reference Manual.

7.1.3. Laboratory Safety Assessment

Haematology, blood chemistry and urinalysis will be drawn at the time points described in the Schedule of Activities (SOA) and analyzed at local laboratories. They may also performed when clinically indicated. The required laboratory tests are listed in Table 8.

Table 8. 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		PTT	
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, total bile acids and acetaminophen drug and/or protein adduct levels.

7.1.4. Vital Signs and Physical Examination

Patients will have a physical exam to include examination of major body systems, weight, blood pressure, pulse rate, assessment of ECOG performance status and height; (height will be measured at screening only) at the time points described in the Schedule of Activities (SOA). 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 standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs at screening, Cycle 1 Day 1 and End of Treatment/Withdrawal. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. Additional ECGs will be performed as clinically indicated. Clinically significant findings seen on the follow-up ECGs should be recorded as adverse events.

7.2. Pharmacokinetics Assessments

Plasma/serum samples will be obtained from patients for PK analysis of axitinib, MK-3475 and anti-MK-3475-antibodies depending on the treatment cohort that they belong to. Samples for MK-3475 PK and anti-MK-3475-antibodies (ADA) will be collected from all patients in the study. Axitinib PK samples will be collected from all patients in the Dose Finding Phase and at least 8 patients in the Dose Expansion Phase.

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.

The PK table indicates PK blood sampling time points for axitinib alone and axitinib in combination with MK-3475. On the days of axitinib PK sample collection, patients should be instructed to hold morning axitinib 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 actual time of axitinib and MK-3475 dosing, as well as actual times of pharmacokinetic collections will be recorded in the source documents and CRF.

Blood samples for axitinib PK, MK-3475 PK and anti-MK-3475 antibodies (ADA) will be collected as outlined in the Schedule for Pharmacokinetic Sample Collections table.

Pharmacokinetic samples for MK-3475 and anti-MK-3475 antibodies will also be collected at 1 month, 3 months and 6 months after end of MK-3475 treatment.

In addition to samples collected at the scheduled times, additional blood samples for axitinib and MK-3475 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. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) will be considered protocol complaint, and the exact time of the sample collection noted on the CRF. If a scheduled blood sample collection cannot be completed for any reason, the missed sample collection may be rescheduled with agreement of clinical Investigators, patient and Sponsor.

PK samples will be assayed for axitinib, MK-3475 and those for anti-MK-3475 antibodies using validated analytical methods. Additional details regarding the collection, processing, storage and shipping of the blood samples will be provided in the study manual. 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, MK-3475 and anti-MK-3475 antibodies (ADA). The results of such analyses may be included in the clinical report.

7.2.2. 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 tube to provide a minimum of 1 mL plasma for pharmacokinetic analysis.

7.2.3. Processing, Storage and Shipment of Axitinib PK Samples

The following special precautions should be taken to minimize the rapid degradation of axitinib 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 MK-3475 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, and MK-3475.

7.2.4. Collection and processing of MK-3475 PK Samples

At each time point 3-mL of blood will be collected into a 3.5 mL Serum Separator Tube (SST) at the designated times. The tube should be inverted 5-6 times without shaking. After collection, sample should be left standing upright at room temperature for 30 minutes but no more than 60 minutes to coagulate. Centrifuge at 1100 to 1300 x g at room temperature for 15 minutes until clot and serum are separated. Serum should be aliquoted into 2 new tubes: Corning 2-mL polypropylene cryovials. Serum samples must be frozen within 30 minutes of collection at –70°C or colder (alternatively –20°C is acceptable for up to 1 month) and maintained in the frozen state until assayed.

7.2.5. Collection and Processing of Anti-MK-3475 Antibody Samples

At each time point 6-mL of blood will be collected into a Serum Separator Tube (SST) at the designated times. Allow blood to remain upright at room temp for at least 30 min but not to exceed 60 min. Centrifuge for 10 to 15 min at 1100 to 1300 x g at room temperature. Collect serum and dispense evenly into two aliquots in polypropylene cryovials. Serum samples must be frozen within 30 min of collection at -70°C or colder (alternatively -20°C is acceptable for up to 1 month) and maintained in the frozen state until assayed.

7.3. Translational and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with MK-3475 when used in combination with a VEGF inhibitor. In addition, analyses of sequentially obtained tissue and blood biomarkers will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment visit will also help understand potential mechanisms of resistance to the drug combination.

7.3.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Tumor biospecimens from archived tissue samples and metastatic lesions (see Section 6.1.1) will be used to analyze candidate DNA, RNA or protein markers, or relevant signature of 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 drug targets such as PD-L1. Studies will investigate whether potential predictive markers represent intrinsic or acquired mechanisms of resistance. Only core biopsies are suitable. Fine needle aspirates are not acceptable. Additional information on tissue collection procedures are included in the study laboratory manual.

7.3.2. Peripheral Blood

Blood biospecimens (10 mL) for serum and whole blood will be obtained from all enrolled patients to measure DNA, RNA, or proteins 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 MK-3475 combination. Markers that may be analyzed include, but may not be limited to VEGF-A, VEGFR2, IL8 and T-cell receptors. Biospecimens should be obtained pre-dose (see Schedule of Activities).

7.4. Banked Biospecimens

7.4.1. Markers of Drug Response

Banked biospecimens will be collected from patients for exploratory research relating to the drug response and disease/condition under study. These collections are not typically associated with a planned assessment described in the protocol.

They will be handled in a manner that protects each patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the patient's ID and the patient's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and 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 for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug development process and also post-marketing research. Patients may withdraw their consent for the use of their banked biospecimens at any time by making a request to the Investigator; in this case, any remaining biospecimen will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses. Unless prohibited by local regulations or ethics committee decision, a 4 mL blood genomic banked biospecimen Prep D1 **(dipotassium edetic acid [ethylenediaminetetraacetic acid]** [K_2 EDTA] whole blood collection optimized for DNA analysis) will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/biomarker analyses related to drug responseand disease under study. 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. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

The Banked Biospecimens will be collected from all patients unless prohibited by local regulations or IRB/EC decision.

It is possible that the use of these biospecimens may result in commercially viable products. Patients will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.4.2. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow the Banked Biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

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 at baseline and when 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 (screening), at 12 weeks, and every 6 weeks thereafter. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 6 weeks). See Schedule of Activities (SOA) and Section 5.2.4.2.1 for treatment after initial evidence of disease progression.

Bone scan (bone scintigraphy) or ^{18}F-FDG-PET/CT is required at baseline then every 12 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. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the Investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below) requiring immediate notification to Pfizer or its designated representative. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a

description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/ legally acceptable representative. In addition, each study patient/ legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal section)

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

When a patient withdraws from the study because of a SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each patient begins from the time the patient provides informed consent, which is obtained before the patient’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 90 calendar days after the last administration of the investigational product.

For patients who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

- If a patient begins a new anticancer therapy, SAEs occurring during the above indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

Pregnancy or breast feeding that occur during the trial, within 120 days of discontinuing treatment with MK-3475, or within 28 days after the cessation of study treatment if the patient begins a new anticancer therapy, whichever is earlier, should be reported as in Section 8.4 (Exposure During Pregnancy).

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non serious AEs and SAEs are recorded on the CRF.

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.

If a patient begins a new anticancer therapy, the recording period for non serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above indicated active collection period.

8.1.5. 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 on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as

defined by the sponsor. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Event

An AE is any untoward medical occurrence in a study 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, AEs 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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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.

8.2.3. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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.

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 on the CRF, and as an SAE with CTCAE Grade 5 (see the section on Severity Assessment).

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even if 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, 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.

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.03 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 patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some patients, transaminase elevations are a harbinger of a more serious potential outcome. These patients fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug induced liver injury (DILI). Patients who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the patient’s individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For patients with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The patient should return to the investigator 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.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over the counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

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

- 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 discontinuation and/or being exposed to the investigational product.

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

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

If a patient or 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 Safety on a CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy outcome and its information for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety 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 to Pfizer Safety 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 EDP may be requested by the sponsor. 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 EDP 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.

8.4.2.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences a SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.2.3. 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 Pfizer Safety unit within 24 hours of the Investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated 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 CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong patient, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

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 MK-3475.

- Per protocol analysis set (evaluable for DLT).

All enrolled patients who are eligible, receive at least one dose of axitinib and MK-3475, and who either experience DLT during the first two cycles, or complete the observation period for the first two cycles of treatment (6 weeks). Patients who withdraw from study treatment before receiving at least 75% of the planned first two cycles doses of axitinib or two infusions of MK-3475 within the DLT observation period due to reasons other than treatment related adverse events are not evaluable for DLT. A patient who is unable to start at the assigned Cycle 1 Day 1 dose level after the lead-in period will not be evaluable for DLTs but will be evaluated for safety and efficacy.

- Response evaluable analysis set.

All patients who receive study treatment with an adequate baseline tumor assessment will be considered evaluable for anti-tumor efficacy using standard RECIST 1.1 criteria.

- PK analysis set.

The PK concentration population is defined as all treated patients who have at least 1 concentration of either 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[23] 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/ de-escalation decisions for a given trial can be pre-calculated under the mTPI design and presented in a two-way table (Table 2). 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.[23]

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 MK-3475, e_1 is selected as 0.05, and e_2 is selected as 0.03. Therefore, the target dosing interval for the DLT rate is (0.25, 0.33).

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 staying 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 patient 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-escalation 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[23] 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 completed when at least 10 DLT-evaluable patients have been treated at the highest dose associated with a DLT rate <0.33. It is estimated that approximately 20 DLT-evaluable patients will need to be enrolled to reach 10 DLT-evaluable patients at the estimated MTD.

9.2.2. Statistical Method for Estimating the MTD

As described in Section 3.2, the estimated MTD will be the highest tested dose level with a DLT rate <0.33 in 10 DLT evaluable patients. We assume that higher doses of MK-3475 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 (MK-3475 2 mg /kg q3wks, axitinib 5 mg BID) may have a higher proportion of observed toxicities than, say, (MK-3475 1 mg /kg q3wks, 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.[24] 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.

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 60 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 design using the mTPI approach cannot be determined in advance. It is estimated 20 DLT evaluable patients will be enrolled in the dose finding stage in order to have a reliable and accurate estimate of the MTD. In addition, there will be a Dose Expansion Phase cohort 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 0.08, ie, by definition,

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

Therefore, a sample of forty patients ($n=40$) in the Dose Expansion Phase cohort will allow estimation of the probability of achieving an event of interest with the standard error ≤0.08. The sample size estimate for the expansion cohort also takes into consideration the key tumor biomarker PD-L1 endpoints. If the observed rate of PD-L1 positives is 20% then approximately 40 patients would be required to enroll 8 PD-L1 positive patients.

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 listings for the Dose Expansion Phase cohort. For the Dose Finding cohorts only data listings for BOR will be presented.

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

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. 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.

Time to Response (TTR) is defined as the time from first dose of study treatment to the first documentation of objective tumor response (CR or PR) that is subsequently confirmed.

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 of study treatment to the first progression of disease (PD) or death for any reason in the absence of documented PD. PFS will be summarized in the response evaluable population. 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 within 28 days of last dose. 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.

Overall Survival (OS) is defined as the time from the first dose of study treatment to the date of death due to any cause. OS will be summarized in the response evaluable population. For patients still alive at the time of the analysis, the OS time will be censored on the last date they were known to be alive. Patients lacking data beyond the day of first dose of study treatment will have their survival times censored at 1 day.

Summaries will include: ORR, TTR, DR, PFS and OS. Time-to event endpoints (TTR, DR PFS and OS) 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), TTR, DR, PFS and OS.

9.5. Analysis of Other Endpoints

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetic Analysis of MK-3475 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 will be estimated using non-compartmental analysis. For axitinib, standard PK parameters will include C_{max}, T_{max}, AUC_{0-12}, oral plasma clearance (CL/F), and apparent volume of distribution (V_z/F) Descriptive statistics for the PK parameters for axitinib will be provided by dose, cycle and day of assessment in tabular form. For MK-3475, pharmacokinetics will be evaluated using population pharmacokinetic modeling.

All plasma/serum 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 MK-3475 will be plotted for each dose using a box-whisker plot by cycle and day 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 for MK-3475.

9.5.1.2. Effect of MK-3475 on Axitinib Pharmacokinetics

The effect of repeated MK-3475 dosing on axitinib PK will be evaluated based on changes in AUC_{0-12} of axitinib on Lead-in Day 7 and Cycle 7 Day 1, respectively, as the primary pharmacokinetic parameter. The associated 90% confidence interval will also be computed to assess the magnitude of the effect.

9.5.1.3. Immunogenecity Assessment

Results for the anti-MK-3475 antibody (ADA) assessment will be provided. The effect of ADA on MK-3475 concentration will be evaluated.

9.5.1.4. Population Pharmacokinetic Analysis or PK/PD Modeling

MK-3475 disposition will be evaluated using a population PK model for the drug. The results of this analysis, if performed, will be reported separately.

9.5.1.5. Statistical Analysis of Biomarker Endpoints

Biomarkers will be assessed separately for blood and tumor tissue biospecimens. 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 90 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 Finding Phase of the study. The occurrence of DLTs observed in the Dose Finding Phase is used to estimate the MTD (if reached) as described in Section 3.2. 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. Single ECG measurement will be obtained at screening and on Cycle 1 Day 1 and End of Treatment/Withdrawal. Additionally, ECGs should be performed when clinically indicated.

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.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee (DMC). 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 escalations 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 Finding 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 are accurate. The Investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

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

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. 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 inspections/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 ICH guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

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

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

The informed consent document(s) and any patient recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

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

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

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

12.4. Patient Recruitment

Advertisements approved by 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 regulatory 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/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of axitinib or MK-3475 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 (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (CSR 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.

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

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

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

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

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

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

16. REFERENCES

1. Gupta K, Miller JD, Li JZ et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008; 34: 193–205.

2. Wierecky J, Muller MR, Wirths S et al. Immunologic and clinical responses after vaccinations with peptide-pulsed dendritic cells in metastatic renal cancer patients. Cancer Res 2006; 66: 5910–5918.

3. Zou, W., and L. Chen. 2008. Inhibitory B7-family molecules in the tumour microenvironment. Nat. Rev. Immunol. 8:467Rev. Ihttp://dx.doi.org/10.1038/nri2326.

4. Ahmadzadeh, M., L.A. Johnson, B. Heemskerk, J.R. Wunderlich, M.E. Dudley, D.E. White, and S.A. Rosenberg. 2009. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood. 114:1537, M., Lhttp://dx.doi.org/10 .1182/blood-2008-12-195792.

5. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N. Engl. J. Med. 366(26), 2443–2454 (2012).

6. Daniel C. Cho, Jeffrey Alan Sosman, Mario Sznol, Michael S. Gordon, Antoine Hollebecque, Omid Hamid, David F. McDermott, Jean-Pierre Delord, Ina Park Rhee, Ahmad Mokatrin, Marcin Kowanetz, Roel Peter Funke, Gregg Daniel Fine, Thomas Powles. Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 31, 2013 (suppl; abstr 4505).

7. David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John Powderly, David C. Smith, Jon Wigginton, Dan McDonald, Georgia Kollia, Ashok Kumar Gupta, Michael B. Atkins. Clinical activity and safety of anti-PD-1 (BMS-936558, MDX-1106) in patients with previously treated metastatic renal cell carcinoma (mRCC). ASCO 2012 annual Meeting.

8. Hutson E., Lesovoy V., Al-shukri S., Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. The Lancet Oncology, Volume 14, Issue 13, Pages 1287 - 1294, December 2013.

9. Rini BI, Escudier B, Tomczak p, et al, comperative effectiveness of axitinib versus sorafenib in advanced renal-cell carcinoma (AXIS): a randomized phase 3 trial. Lancet 2011; 378: 1931-39.

10. Ferrar N. Kerbel R. S. 2005 Angogenesis as a therapeutic target. *Nature* 438:967.

11. Ellis L.M. Hicklin D.J. 2008 VEGF-targeted therapy: Mechanisms of anti-tumor activity. *Nat. Rev. Cancer* 8:579.

12. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society; 2013.

13. Choueiri T.K., Vaishampayan U., Rosenberg J.E., *et al* 2013 Phase II and Biomarker Study of the Dual MET/VEGFR2 Inhibitor Foretinib in Patients with Papillary Renal Cell Carcinoma *J. Clin. Oncol.* 31:181-186.

14. Finley D.S., Pantuck A.J., Belldegrun A.S. 2011 Tumor Biology and Prognostic Factors in Renal Cell Carcinoma. *The Oncologist*, 16:4.

15. NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Version 1.2013.

16. Gross-Goupil M., Massard C., Ravaud A. 2012 Targeted Therapies in Metastatic Renal Cell Carcinoma: Overview of the Past Year *Curr. Urol. Rep.* 13:16-23.

17. Mihaly Z., Sztupinszki Z., Surowiak P., and Gyorffy B. 2012 A Comprehensive Overview of Targeted Therapy in Metastatic Renal Cell Carcinoma *Current Cancer Drug Targets* 12:857-872.

18. Escudier B., Albiges L., and Sonpavde G. 2013 Optimal Management of Metastatic Renal Cell Carcinoma: Current Status *Drugs* 73:427-38.

19. Investigator's Brochure of AG-013736, dated November 2013.

20. Investigator's Brochure of MK-3475, dated 10 January 2014.

21. Hamid O.et al Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma, N Engl J Med (2 June 2013), doi:10.1056/nejmoa1305133 Key:citeulike:12397700.

22. United States Package Insert for Inlyta®, dated January 2012.

23. Ji Y et al. A modified toxicity probability interval method for dose-finding trials. *Clinical Trials* 2010; 7:653 663.

24. Dykstra R, Robertson T. An algorithm for isotonic regression for two or more independent variables. Ann Stat. 1982;10:708-716.

25. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28 (29):4531-8.

26. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8 (8):793-800.

27. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

28. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

29. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

30. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

31. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

32. Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

33. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

34. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

35. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

36. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

37. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

38. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

39. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

40. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10(840):841.

41. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

42. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

43. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

44. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

45. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

46. 2006. Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. J. Cin Oncol Jul 1:3187-3205.

47. Larochelle P., Kollmannsberger C., Feldman R.D., et al. 2012 Hypertension management in patients with renal cell cancer treated with anti-angiogenic agents. Curr. Oncol 19:202-208.

48. Brian I. Rini, David I. Quinn, Michael Baum, Laura S. Wood, Jamal Tarazi, Brad Rosbrook, Lillian Shahied Arruda, Laura Cisar, W. Gregory Roberts, Sinil Kim, Robert J. Motzer. Hypertension among patients with renal cell carcinoma receiving axitinib or sorafenib: analysis from the randomized phase III AXIS trial. Targ Oncol DOI 10.1007/s11523-014.

49. A.Amin, E.R. Plimack, J.R. Infante, et al. Nivolumab (anti-OD1; BMS-936558; ONO-45380 in combination with sunitinib or pazopanib in patients with metastatic renal cell carcinoma (mRCC). Abstract 5010, ASCO 2014.

50. Poole, R.M., Pembrolizumab: First Global Approval. Drugs, 2014.

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 Version 1.1

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

Measurability of Tumor Lesions

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

Measurable:

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

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

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

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

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

Recording Tumor Measurements

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

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

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

Techniques for Assessing Measurable Disease

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

Definitions of Tumor Response

Target Lesions

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

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

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

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

Non-Target Lesions

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

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

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

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

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 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 12 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
BCG	Bacillus Calmette–Guérin
BID	Twice/day
BOR	Best Oveall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatinine kinase
CL	Clearance
Cmax	Maximum plasma Concentration
Cmin	Minimum plasma Concentration
CR	Complete Response
CRF	Case Report Form
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
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
ECI	Event of Clinical Interest
EIU	Exposure in Utero
EU	Europe
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded
FH	Fumarate Hydratase
GCP	Good Clinical Practice

GGT	Gamma-Glutamyl Transferase
GI	Gastro-intestinal
HCV	Hepatitis C Virus
HCV	Hepatitis C Virus
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
irAE	Immune-related adverse event
IRB	Institutional Review Board
IUD	Intra Uterine Device
IV	Intravenous
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
PD1	Programmed Death 1
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PD-L1	Programmed Death Ligand 1
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
TBili	Total Bilirubin
TIL	Tumor Infiltrating Lymphocytes
TIDM	Type 1 Diabetes Mellitus
TKI	Tyrosine Kinase Inhibitor
Tmax	Time to maximum plasma concentration
TSH	Thyroid Stimulating Hormone
TTR	Time To Response
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. KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund: fatal processes progressing rapidly
	0	Dead

Reference:
http://www.npcrc.org/usr_doc/adhoc/functionalstatus/Karnofsky%20Performance%20Scale.pdf

Appendix 6. Revised Schedule of Activities Following Collection of Data for Primary Study Objective

After the collection of data for the primary study objective and most of the secondary objectives has been completed, patients who are still clinically benefiting from study treatment as judged by the investigator may be candidates for continuation of study treatment. Discussion with sponsor is required.

The following protocol sections should be disregarded: Schedule of Activities the original protocol and the trial procedures in Section 6.2 Study Period, 7.2 Pharmacokinetics Assessments, 7.2.1 Blood Sample Collection for Pharmacokinetic Analysis, 7.2.2 Collection of Axitinib PK Samples, 7.2.3 Processing, Storage and Shipment of Axitinib PK Samples, 7.2.4 Collection and Processing of MK-3475 PK Samples, 7.2.5 Collection and processing of anti-MK3475 Antibody Samples, and 7.3 Translational and Pharmacodynamic Assessments. The investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Activities table in order to conduct evaluations or assessments required to protect the well-being of the patient.

The following schedule of activities will be implemented for patients still on active treatment and long-term survival follow-up. Patients on axitinib monotherapy have the opportunity to continue axitinib treatment on a Pfizer-sponsored patient access program at the time of the discontinuation of survival status follow-up.

	Study Treatment[1]	**Post-Treatment**		
Protocol Activities and Forms to be Completed	**Cycles ≥24** **Day 1 –3/+3**	**End of Tx or Withdrawal**[2] **–3/+3**	**28 Days Post-Treatment –7/+7**	**Survival Follow-Up –7/+7**
Physical Examination [3]	X	X		
In Clinic Blood Pressure, Pulse Rate [4]	X	X		
Home Blood Pressure Monitoring[5]	X	X		
Hematology [6]	Local Standard of Care	X		
Blood Chemistry [6]	Local Standard of Care	X		
Coagulation [6]	Local Standard of Care			
Urinalysis [7]	X			
12-lead ECG [8]	X	X		
Thyroid Function Tests [9]	X	X		
Pregnancy Test [10]	X	X		
Tumor Assessments [11]	Local Standard of Care and at End of Treatment			
Adverse Events [12]	X	X	X	
Concomitant Medications/Treatments(13)	X	X	X	
Study Treatment (14)	X			
Post Study Survival Status (15)			X	X

Footnotes for Schedule of Activities	
1.	During Treatment: All assessments should be performed prior to dosing with study treatment unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. Patients who permanently discontinue pembrolizumab and continue on axitinib treatment, it is at the discretion of the investigator to follow patients on axitinib monotherapy every 3 weeks + or – 3 days (ie, cycle=21 days) or 6 weeks + or – 3 days (ie, cycle=42 days). All tests and assessments outlined in the schedule of activities must be conducted at that visit.
2.	End of Study Treatment/Withdrawal: Obtain these assessments if not completed during the previous two weeks on study.
3.	Physical Examination: Includes an examination of major body systems and weight.
4.	In Clinic 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.
5.	Home blood pressure monitoring: All patients will receive home blood pressure monitoring devices and blood pressure will be monitored at home. While on axitinib (as single agent or combined with MK 3475) patients 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 5.2.7.3).
6.	Hematology, Blood Chemistry, and Coagulation: Required tests are listed in Table 8. All laboratory tests may be performed per standard of care and when clinically indicated. Dose adjustment may be required (see Section 5.2.7).
7.	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 5.2.7.2). May be performed also when clinically indicated.
8.	Single ECG measurement will be obtained at End of Treatment/Withdrawal. Additionally, ECGs should be performed when clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
9.	Subsequently, TSH should be assessed every 6 weeks thereafter starting from Cycle 24 Day 1. Free T3 and free T4 should additionally be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.
10.	For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed and routinely repeated at every 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. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations (see Section 7.1.1).
11.	Tumor assessments will include all known or suspected disease sites: frequency to be performed per local standard of care and again at treatment withdrawal if not performed within previous 6 weeks. Tumor imaging must be measured using RECIST version 1.1 tumor assessment criteria to determine disease progression.
12.	Adverse Events: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product and before initiation of a new anti-cancer treatment. The prolonged follow up is due to the pharmacokinetic properties of the investigational product MK-3475. SAEs experienced by a patient after the active reporting period (see Section 8.1.4) 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 study drug 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. Pregnancy or breast feeding that occur during the trial, within 120 days of discontinuing treatment with MK-3475, or within 28 days after the cessation of axitinib if the patient begins a new anticancer therapy, whichever is earlier, should be reported as in Section 8.4.2.1 (Exposure During

	Pregnancy).
13.	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).
14.	Study treatment: will be administered as in Section 5.2.4.2.1 Axitinib will be given orally twice daily PO on a continuous schedule. MK-3475 will be given as a 30 minute intravenous infusion every 3 weeks. (one Cycle = 3 weeks) (see Section 5). Patients with disease progression who are continuing to derive clinical benefits from the study treatment may continue treatment with axitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable and after discussion with the sponsor. Continuation of treatment with MK-3475 beyond 24 months should be discussed with the sponsor and not go beyond 36 months. Patients who permanently discontinue pembrolizumab and continue on axitinib treatment, it is at the discretion of the investigator to follow the patient on axitinib monotherapy every 3 weeks + or – 3 days (ie, cycle=21 days) or 6 weeks + or– 3 days (ie, cycle=42 days). All tests and assessments outlined in Appendix 6 Schedule of Activities must be conducted at that visit or when clinically indicated. Patients on axitinib monotherapy have the opportunity to continue axitinib treatment on a Pfizer-sponsored program at the time of the discontinuation of survival status follow-up.
15.	Survival: All patients should be followed for survival at least every 3 months after discontinuing study treatment. Survival monitoring will continue until approximately 3 years after last patient has been enrolled. Information on antineoplastic treatments (ie, systemic, surgery, and radiotherapy) will be collected.