CLINICAL PROTOCOL

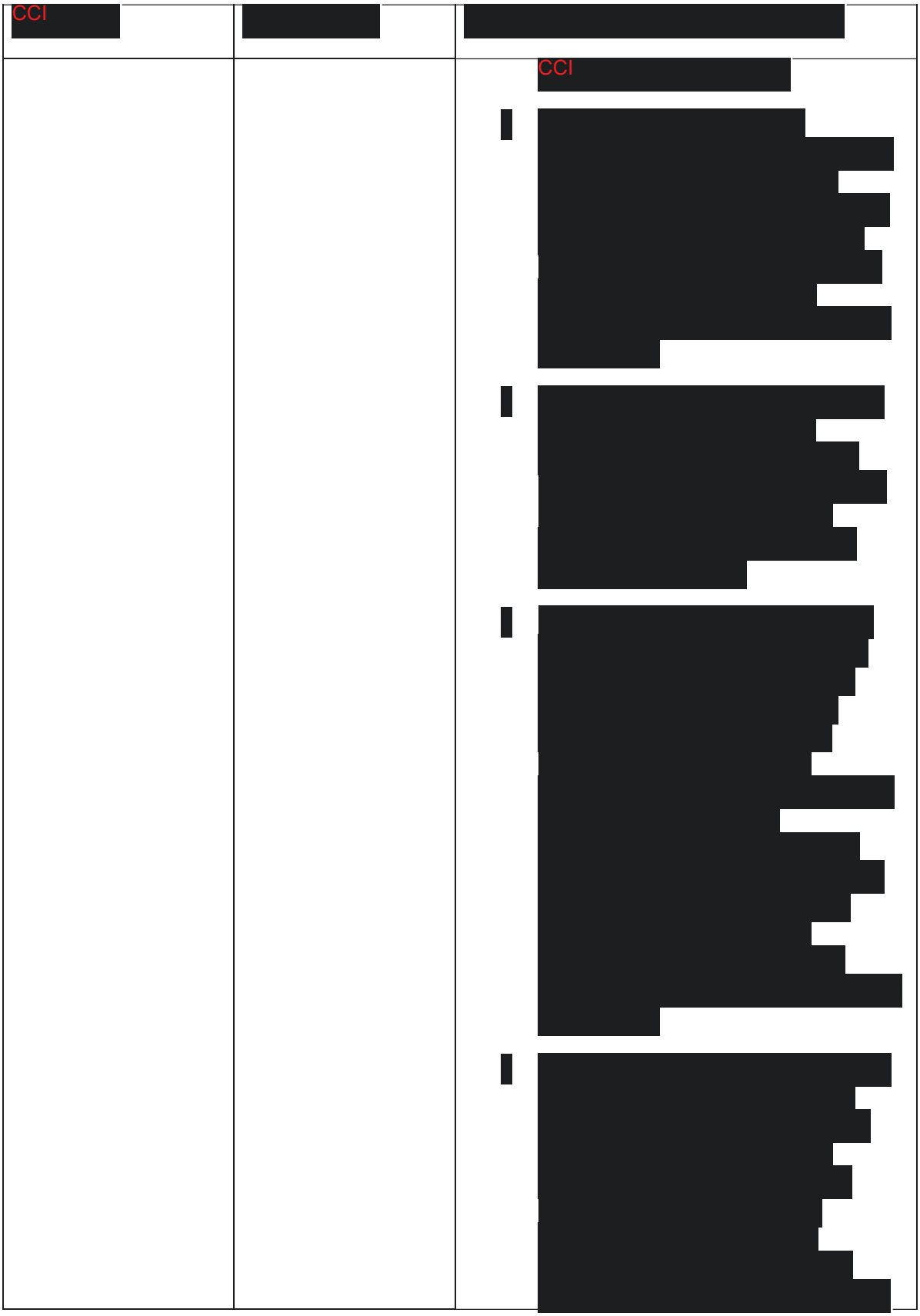
RENAL CELL CARCINONA – JAVELIN RENAL 100

A PHASE 1B, OPEN-LABEL, DOSE-FINDING STUDY TO EVALUATE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF AVELUMAB (MSB0010718C) IN COMBINATION WITH AXITINIB (AG-013736) IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED RENAL CELL CANCER

Compounds:	MSB0010718C, AG-013736
Compound Names:	Avelumab, Axitinib
US IND Numbers:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number :	2015-001137-25
Protocol Number:	B9991002
Phase:	1b

[redacted]

Document History



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] RCC is often first detected at an advanced stage, with 25-30% of patients having metastatic disease at diagnosis. Until 2005, interferon-alpha (IFN-α) and high-dose interleukin (IL)-2 therapies were the standards of care for patients with advanced RCC (aRCC), albeit with modest efficacy. Since then, development and approval of multiple vascular endothelial growth factor (VEGF) pathway 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, durable and complete responses in aRCC patients are uncommon; the majority of patients will eventually develop resistance, exhibit disease progression while on therapy, and succumb to death due to metastatic disease. Response rates for previously treated aRCC patients are in the 15-25% range, and median survival after diagnosis is under 1 year.[1]

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.[16] These reports have generated considerable interest in immunotherapeutic approaches in the treatment of aRCC patients, especially with advent of immune checkpoint inhibitors such as anti-programmed cell death protein-1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) monoclonal antibodies in recent years. Upregulation of PD-1 receptor on tumor-infiltrating lymphocytes (TILs), and its ligand PD-L1 on tumors, are associated with more aggressive disease and poor prognosis.[17,18]

Monoclonal antibodies (mAb) that block the PD-1/PD-L1 interaction are novel immunotherapeutic approaches for aRCC, which have shown single-agent efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy.[19,20] Nivolumab, a high-affinity, fully human anti-PD-1 mAb has shown durable tumor responses with objective response rate (ORR) of about 20% and median progression-free survival (PFS) of about 16 weeks in heavily pretreated aRCC patients.[21,22] When nivolumab was combined with a VEGF TKI (sunitinib or pazopanib), it demonstrated more pronounced anti-tumor response. Amin et al reported the data from combinations of sunitinib or pazopanib with nivolumab at the American Society of Clinical Oncology (ASCO) 2014 annual meeting.[23] The pazopanib plus nivolumab arm was discontinued due to safety issues; however, sunitinib (50 mg, 4 weeks on/2 weeks off) was successfully combined with nivolumab 5 mg/kg every 3 weeks (Q3W), and dose expansion was subsequently completed in previously untreated aRCC patients. ORR was 52% (17/33) for nivolumab in combination with sunitinib, and 45% (9/20) for nivolumab in combination with pazopanib. Median duration of response (DR) was 37.1 weeks (95% confidence interval [CI]: 18.1-80.0+), and median PFS was 48.9 weeks (95% CI: 41.6-66.0) with sunitinib plus nivolumab.

MPDL3280A, another human mAb that targets PD-L1, has shown ORR of 13% and stable disease (SD) ≥24 weeks in 32% of patients with previously treated RCC when administered as a single agent. Results from the combination of bevacizumab 15 mg/kg Q3W with MPDL3280A (20 mg/kg) were presented by McDermott et al at the European Society for Medical Oncology (ESMO) 2014 annual meeting.[24] Data were limited, but in previously untreated aRCC patients, there were 4 of 10 (40%) patients who had partial responses (PRs). Five additional patients had a best response of SD, and almost all (9 out of 10) responding patients were still on treatment at the time of analysis. These data, although preliminary, demonstrate the benefit of combining an anti-PD-1 or PD-L1 antibody with an anti-VEGF pathway agent in aRCC patients.

The combination of nivolumab with ipilimumab, a fully human monoclonal antibody to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed acceptable safety and encouraging antitumor activity in patients with metastatic RCC. Patients were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (Arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (Arm N1 + I3) intravenously (IV) Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity. Confirmed objective response (OR) was observed in 9/21 patients in Arm N3 + I1 and in 11/23 patients in Arm N1 + I3. The median PFS was 36.6 weeks and 38.3 weeks in Arm N3 + I1 and in Arm N1 + I3, respectively.[25]

Avelumab (MSB0010718C) is a fully human mAb of the immunoglobulin (Ig) G1 isotype that specifically targets and blocks PD-L1.[26] Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody MSB0010718C.

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as a single agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

As of 05 November 2015, more than 1400 patients have been treated with avelumab. The largest trial is study EMR100070-001, a Phase 1, open-label, multiple ascending-dose clinical study aimed to investigate the safety, tolerability, pharmacokinetics (PK), biological activity, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. Study EMR100070-001 consists of 2 parts, a dose-escalation phase and a dose-expansion phase, the latter performed in selected tumor indications. Avelumab is administered intravenously (IV) at the assigned dose level as a 1-hour infusion once every 2 weeks (Q2W).

In the Phase 1 study EMR 100070-001, 53 patients have been treated with avelumab doses of 1.0, 3.0, 10.0, and 20.0 mg/kg administered IV every 2 weeks (Q2W) in the dose escalation phase. In the subsequent dose expansion phase, 1300 patients in the pooled malignancies with different tumor types have been treated at a dose of 10 mg/kg Q2W.

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Preliminary Safety Data of Avelumab as Monotherapy in aRCC

In the aRCC cohort of the Phase 1 study EMR 100070-001, 18 patients with aRCC in the second-line and beyond treatment setting received avelumab IV Q2W at the dose of 10 mg/kg (see Section 1.2.2.1).[9] Current data indicate that the safety profile of the aRCC cohort is consistent with that of the overall population of study EMR 100070-001. Since December 2015, an additional cohort of approximately 30 patients with aRCC in the first-line treatment setting has started enrollment within the EMR 100070-001 study.

Axitinib is an oral, potent and selective inhibitor of VEGFRs 1, 2, and 3 approved multinationally for the treatment of aRCC after failure of one prior systemic therapy (actual indication varies according to region/country).[10] The antitumor activity of single-agent axitinib 5 mg twice daily (BID) in previously untreated 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 PFS, axitinib was associated with a longer median PFS (mPFS) time (mPFS 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 (HR) 0.77 [95% CI: 0.56, 1.05]).[13] The mPFS observed with axitinib in this study was similar to those demonstrated earlier in Phase 3 clinical trials of other approved VEGFR TKIs in the first-line treatment of aRCC patients. Toxicities in this clinical trial were generally tolerable and manageable, and similar to those observed in clinical trials with axitinib in pre-treated aRCC patients.[13]

The most common adverse events (>20% of patients) reported among 1445 cancer patients receiving single-agent axitinib (regardless of causality) included diarrhea, hypertension, decreased appetite, nausea, weight decreased, dysphonia, palmar plantar erythrodysaesthesia syndrome, hypothyroidism, and proteinuria. The most frequent Grade ≥3 adverse events were hypertension, fatigue, and diarrhea.[11] The risk of hepatotoxicity was low in patients with aRCC with axitinib, with an overall rate of Grade 3/4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased <0.6% for each.[27] The incidence of hematological toxicity was also low for axitinib in this patient population (eg, Grade 3/4 platelet count decreased and neutrophil count decreased 0.3% for each).[27]

Based on the observations above, it is proposed that the addition of the PD-L1 inhibitor avelumab to the VEGF pathway inhibitor axitinib may provide additional clinical benefit compared to treatment with an anti-VEGFR TKI alone without unacceptable toxicity in previously untreated aRCC patients leveraging their complementary mechanisms of action. The combination of avelumab with axitinib has not been previously studied in patients; therefore, there are currently no safety data from this combination. There are no expected overlapping toxicities between avelumab and axitinib, except for fatigue, nausea/diarrhea, and hypothyroidism, which are usually low-grade events easily manageable following the adverse event management guidelines implemented in the study protocol. Additional safety concerns are not expected from combining avelumab with axitinib given their distinct mechanisms of action and toxicity profiles.

Overall, the observed benefit-risk profile supports the further investigation of avelumab in combination with axitinib in the patient population chosen for this study.

This clinical study, therefore, is designed to determine the recommended doses as well as the preliminary safety, pharmacokinetics (PK), and efficacy of this combination regimen needed to support a subsequent randomized clinical trial of avelumab in combination with axitinib versus VEGFR TKI in the first-line aRCC treatment setting.

Study Objectives:

Primary Objective

- To assess the safety and tolerability of avelumab in combination with axitinib 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 avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To assess the preliminary anti-tumor activity of avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To evaluate the overall survival (OS) of avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To characterize the PK of avelumab and axitinib when administered in combination, and to assess the effect of avelumab on the PK of axitinib.
- To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib.
- To assess the immunogenicity of avelumab when combined with axitinib.

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Study Endpoints:

Primary Endpoint

- DLTs within the first 4 weeks (2 cycles) of treatment with avelumab in combination with axitinib.

Secondary Endpoints

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 4).
- Vital signs (blood pressure, pulse rate).
- Objective Response (OR) and Disease Control (DC) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 2).
- Time-to-event endpoints: Duration of Response (DR), Progression-Free Survival (PFS), and Time to Tumor Response (TTR).
- Overall Surival (OS).
- PK parameters including C_{max}, T_{max}, AUC_{tau}, and $t_{1/2}$ as appropriate for axitinib; C_{trough} and C_{max} for avelumab.
- Tumor tissue biomarker status (ie, positive or negative based on, for example, PD-L1 expression and/or quantitation of tumor-infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry [IHC]).
- Anti-drug antibodies (ADAs; neutralizing antibodies [Nabs]) of avelumab when combined with axitinib.

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Study Design:

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of avelumab in combination with axitinib in adult patients with previously untreated aRCC. This clinical study will be composed of a Dose Finding Phase and a Dose Expansion Phase.

The Dose Finding Phase will estimate the MTD and RP2D in patients with aRCC with clear cell histology who did not receive prior systemic therapy for advanced disease, using the modified toxicity probability interval (mTPI) method.[29] Dose finding will follow an mTPI design, with up to 3 potential dose levels (DL) to be tested:

- (DL1) avelumab 10 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1A) avelumab 5 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1B) avelumab 10 mg/kg Q2W + axitinib 3 mg BID.

DL-1A and DL-1B will be explored concurrently in a randomized fashion only if the MTD is exceeded in DL1.

To understand the extent of any effects of avelumab on axitinib PK, 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 of the study. Since avelumab has a half-life of 3-5 days, it would not be feasible to run a lead-in with avelumab alone to study the PK of avelumab alone. Therefore, the effect of axitinib on avelumab will be evaluated by comparing avelumab trough concentrations at steady state in the presence of axitinib with those reported for avelumab alone in prior studies.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for avelumab in combination with axitinib in patients with aRCC who did not receive prior systemic therapy for their advanced disease. The Expansion Test Dose will either be the MTD (ie, the highest dose of avelumab and axitinib 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 avelumab in combination with axitinib will be evaluated in up to 20-40 patients with previously untreated aRCC.

Based on the emerging PK data, and after completion of the dose-finding part of the study based on the mTPI method, it may be necessary to enroll up to approximately 8 additional patients to further assess the effect of avelumab on the PK of axitinib. These additional patients will undergo the same evaluations and procedures as those described in the Schedule of Activities table for the Dose Finding Phase of the study and will be treated concurrently with the initiation of the Dose Expansion Phase of the study. With the exception of the mTPI-related assessments leading to determination of MTD, any other assessments or procedures described for the Dose Finding Phase will also apply to these additional patients.

Throughout the course of the study, patient safety will be closely monitored by the sponsor's study team. The number of patients to be enrolled in the Dose Finding Phase will depend on the observed safety profile, and the number of tested dose levels.

All patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy. Patients who do not return to the site should be contacted by telephone every 3 months as an alternative.

Study Treatment:

Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule. Avelumab will be given as a 1-hour IV infusion Q2W. All patients will continue treatment with study drugs until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.4).

Patients will be monitored closely for toxicity, and in the event of significant toxicity, dosing of one or both drugs may be modified. Specifically, avelumab doses may be omitted or permanently discontinued, and axitinib doses may be delayed, reduced or permanently discontinued, as per Section 5.3.5. 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 5.3.5.3). Avelumab treatment modification for drug-related toxicities, including immune-related adverse events (irAEs) and infusion-related adverse events (AEs) is described in Section 5.3.5.

In the Dose Finding Phase, intrapatient axitinib dose escalation is not permitted, except for patients treated at DL-1B. In these patients, after the completion of the primary DLT observation period, intrapatient axitinib dose escalation may occur according to the criteria described in Section 5.3.5.1. In the Dose Expansion Phase, intrapatient axitinib dose escalation may occur if the intrapatient escalation criteria are met (see Section 5.3.5.1).

Patients who stop one of the two study drugs (avelumab or axitinib) for reasons other than confirmed disease progression may continue on single-agent treatment with the other drug until disease progression (RECIST v.1.1), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is prematurely terminated by the sponsor, whichever comes first. Patients who are still deriving clinical benefit following continued treatment for

more than 2 years will be provided an option for continued study treatment (eg, a rollover study).

Patients who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression thereafter will be eligible for re-treatment with avelumab at the discretion of the investigator and after discussion with the sponsor's medical monitor if 1) no cancer treatment was administered other than axitinib since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, and 3) the trial is still open. Patients will resume avelumab therapy at the same dose and schedule applied at the time of discontinuation.

Patients who develop disease progression on study treatment but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab combined with axitinib, single-agent avelumab, or single-agent axitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Statistical Methods:

Dose finding will follow the mTPI method,[29] using doses of avelumab and axitinib.

The escalation/de-escalation rules will follow the 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. However, patients may be enrolled in cohort sizes of 3-4 depending on the number of potential patients identified at participating sites. The patients treated at each dose level may initiate dosing simultaneously. 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.
- The next cohort may be enrolled when all patients at the current dose cohort have been evaluated for 4 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 2 cycles of axitinib or 2 infusions of avelumab 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 6 DLT-evaluable patients have been treated at the highest dose associated with DLT rate <0.33. It is estimated that approximately 15 DLT-evaluable patients will need to be enrolled to reach 6 DLT-evaluable patients at the estimated MTD.

- 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, PK, and pharmacodynamics (PD) involving all available data from test cohorts.

Sample Size Determination

The sample size planned for the dose finding phase arises from logistic feasibility and is not entirely driven by statistical considerations. Due to the dynamic nature of the dose allocation procedure and unknown safety profile of the combination, the sample size of the interval design cannot be determined in advance. It is expected that approximately 15 DLT-evaluable patients will be required for the dose finding phase.

Up to approximately 40 patients will be included in the dose expansion phase of the study for each MTD dose level cohort expanded. A sample size of 40 patients will provide at least 90% probability to observe at least 1 AE if the true incidence of the AE in the population is ≥6%.

Dose-Finding Criteria

Dose finding will follow the mTPI design, using doses of avelumab and axitinib as shown below.

Dose Levels in the Dose Finding Phase

Dose Level	Avelumab	Axitinib
1 (Starting Dose Level)	10 mg/kg IV Q2W	5 mg oral BID
-1A	5 mg/kg IV Q2W	5 mg oral BID
-1B	10 mg/kg IV Q2W	3 mg oral BID

BID: twice daily; Q2W: every 2 weeks

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

Based on the emerging PK data and after the completion of the dose-finding part of the study based on mTPI method, it may be necessary to enroll up to approximately 8 additional patients to further assess the effect of avelumab on the PK of axitinib. These additional patients will undergo the same evaluations and procedures as those described in the Schedule of Activities for the Dose Finding Phase of the study and will be treated concurrently with the initiation of the Dose Expansion Phase.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

SCHEDULE OF ACTIVITIES for SCREENING and STUDY TREATMENT Periods
Patients participating in Dose Finding Phase and up to 8 additional patients enrolled for further PK assessment

Visit Identifiers[1]	Screening	Lead-In PK Period (Single-Agent Axitinib)[2]		Study Treatment (1 cycle = 14 days)					
				Cycle 1		Cycle 2		Cycles ≥3 (until amend. #4 approval)	Cycles ≥3 (after amend. #4 approval)
	≤28 Days Prior to Enrollment	Day 1	Day 7	Day 1	Day 8 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)	Day 1 (±3 days)	Day 1 (±3 days)
Clinical Assessments									
Informed Consent[3]	X								
Medical/Oncological History[4]	X								
Baseline Signs/Symptoms[5]		X							
Physical Examination[6]	X			X	X	X	X	X	X (Q6W)
Contraception Check[7]	X	X		X		X		X	X (Q6W)
ECOG Performance Status	X	X		X	X	X	X	X	X (Q6W)
Vital Signs[8]	X	X	X	X	X	X	X	X	X (Q6W)
Home Blood Pressure Monitoring[9]		X							
Laboratory Studies									
Hematology[10]	X	(X)		X	X	X	X	X	X (Q6W)
Blood Chemistry[10]	X[11]	(X)[11]		X[11]	X[11]	X[11]	X[11]	X[11]	X[11] (Q6W)
Coagulation[10]	X	(X)		X	X	X	X	X	If clinically indicated
Thyroid Function Tests[12]	X	(X)						Cycles 4,7, 13, then Q12W	
ACTH[13]	X							X (Cycle 6, then Q12W)	
HBV, HCV Tests	X	If clinically indicated							

Visit Identifiers[1]	**Screening**	**Lead-In PK Period (Single-Agent Axitinib)**[2]		**Study Treatment (1 cycle = 14 days)**					
				Cycle 1		**Cycle 2**		**Cycles ≥3 (until amend. #4 approval)**	**Cycles ≥3 (after amend. #4 approval)**
	≤28 Days Prior to Enrollment	**Day 1**	**Day 7**	**Day 1**	**Day 8 (±1 day)**	**Day 1 (±3 days)**	**Day 8 (±1 day)**	**Day 1 (±3 days)**	**Day 1 (±3 days)**
Serum/Urine Pregnancy Test[14]	X	X		X		X		X	
Urinalysis[15]	X			X				X (Cycle 3, then every odd cycle)	X (Q12W)
12-Lead ECG[16]	X		X	X				X (Cycle 4)	
Disease Assessments									
Tumor Assessments (including scans)[17]	X			Q6W after Cycle 1 Day 1 up to 1 year after the first dose; Q12W thereafter					
Other Clinical Assessments									
Follow-up for Axitinib Dosing Compliance[18]					X[18] (D5 ±3 days)	X[18] (D5 ±3 days)		X[18] (D5 ±3 days)	
Adverse Events[19]		X							
Concomitant Medications/Treatments[20]	X	(X)	X	X	X	X	X	X	X
Enrollment by Study Treatment[21]									
Avelumab[22]				X[21]		X[21]		X[21]	
Axitinib[22]		X							
Other Samplings									
Pharmacokinetics[23]			X	X	X	X		X (Cycles 3, 4, 6, 8, then Q12W, until cycle 50)	
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Mandatory Archival FFPE Tumor Tissue[25]	X								

Visit Identifiers[1]	Screening	Lead-In PK Period (Single-Agent Axitinib)[2]		Study Treatment (1 cycle = 14 days)					
				Cycle 1		Cycle 2		Cycles ≥3 (until amend. #4 approval)	Cycles ≥3 (after amend. #4 approval)
	≤28 Days Prior to Enrollment	Day 1	Day 7	Day 1	Day 8 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)	Day 1 (±3 days)	Day 1 (±3 days)
Mandatory Recent or *De Novo* FFPE Tumor Tissue Block[26]	X								
Anti-Avelumab Antibodies and Neutralizing Antibodies[27]				X		X		X (Cycles, 3, 4, 6, 8, then Q12W, until cycle 50)	

ACTH = adrenocorticotropic hormone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks.

Footnotes for Schedule of Activities for SCREENING and STUDY TREATMENT Periods
Patients participating in Dose Finding Phase and up to 8 additional patients enrolled for further pharmacokinetic (PK) assessment

1. **Visit Identifiers:** All assessments should be performed prior to the start of study treatment unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers.
2. **Lead-In PK Period:** All patients in the Dose Finding Phase and up to approximately 8 additional patients enrolled for further PK assessment.
3. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.
4. **Medical/Oncological History:** To include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery, and radiation therapy.
5. **Baseline Signs/Symptoms:** To be recorded predose on Lead-in Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment.
6. **Physical Examination:** Includes an examination of major body systems and weight (height included at Screening only).
7. **Contraception Check:** Male patients with female partner of childbearing potential and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

8. **Vital Signs:** Vital signs to include: 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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit. After amendment #4 approval, required every 6 weeks.
9. **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 a single agent during the Lead-in PK period and in up to 8 patients enrolled for further PK assessment, or when combined with avelumab), 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 disturbances), although a different blood pressure threshold for contacting the site may be used according to the investigator's clinical judgment (see Section 5.3.5.2).
10. **Hematology, Blood Chemistry, and Coagulation: Required** tests are listed in Table 8. May also be performed when clinically indicated.
11. Blood Chemistry: Full chemistry panel (required tests are listed in Table 8) is required as follows: at Screening, Day 1 of Lead-in PK Period (if not performed in prior 3 days), Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks thereafter. Core chemistry panel (required tests are listed in Table 8) is required as follows: on Cycle 1 Day 8, Cycle 2 Day 8, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 2 weeks thereafter. If full and core chemistry panels are scheduled at the same visit, only the full chemistry panel will be performed. After amendment #4 approval, required every 6 weeks. Required tests are listed in Table 8.-
12. **Thyroid Function Tests:** free T4 and TSH will be performed at Screening, Lead-in Day 1 (only if not performed in prior 3 days), Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 13 Day 1, and then Q12W thereafter. Additional tests should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.
13. **ACTH**: ACTH tests will be performed at Screening, Cycle 6 Day 1, then Q12W thereafter. Additional tests should be performed when clinically indicated. See Table 8.
14. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at up to three occasions prior to starting combination study treatment: once at the start of screening, once at Lead-in Day 1 immediately before axitinib administration, and at the Cycle 1 Day 1 visit immediately before the administration of avelumab in combination with axitinib. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle during the active treatment period and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations (see Section 7.1.1).
15. Urinalysis: Required at Screening, at Cycle 1 Day 1 and then at Day 1 of every odd cycle and at the End of Treatment. After amendment #4 approval, required every 12 weeks. If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein will have to be quantified by 24-hour urine collection. To be performed as clinically indicated at other time points. See Table 8.
16. **12-Lead Electrocardiogram (ECG)**: See Section 7.1.5 for details. ECG measurements will be obtained at Screening, Lead-in Day 7, Cycle 1 Day 1, and Cycle 4 Day 1. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). Triplicate ECGs at Lead-in Day 7 and Cycle 4 Day 1 will be collected pre-dose and at 2 hours post-axitinib dosing. Triplicate ECGs at Cycle 1 Day 1 will be prior to avelumab infusion and within 30 minutes post end of -infusion. When coinciding with blood samples draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic adverse event (AE; eg, syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

17. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET, required at baseline then 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 complete response for patients who have bone metastases. See Section 7.6. The CT and MRI 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, at 6 weeks after the first dose of therapy (ie, Cycle 1 Day 1), then every 6 weeks up to 1 year from the first dose of therapy and every 12 weeks thereafter until confirmed disease progression regardless of initiation of subsequent anti-cancer therapy. Assessments will be performed according to calendar days, regardless of treatment delays or interruptions. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected progressive disease [PD], symptomatic deterioration, etc.). Complete response (CR) and partial response (PR) must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD unless clinical deterioration occurs. Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 CCI [redacted]. See Section 7.6 for additional information.

18. **Follow-up for Axitinib Dosing Compliance:** Follow-up by telephone will be done to confirm patient understanding and compliance with dosing instructions on Cycle 1 Day 5. Axitinib dosing compliance will also be assessed following any dose modification. If needed, patients will be retrained.

19. **Adverse Events:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Advers Events (CTCAE) version 4.03. After amendment #4 approval, patients receiving axitinib single agent will visit the site every 6 weeks. Between site visits, AEs collection will be performed every 2 weeks by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. For serious adverse events (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 study treatment, through and including 90 calendar days after the last dose of study treatment. SAEs occuring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the 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 1 dose of study treatment through and including 90 calendar days after the last dose of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.

20. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). After amendment #4 approval, patients receiving axitinib single agent will visit the site every 6 weeks. Between site visits, concomitant medication collection will be performed every 2 weeks by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.

21. **Enrollment:** Patient number and dose level allocation will be operated by the sponsor (see Section 5.1). Required information: site and patient identifiers and demographic information. Study treatment should begin within 3 days after enrollment.

22. **Study Treatment:** Axitinib will be given orally (PO) twice daily (BID) on a continuous schedule. Avelumab will be given as a 1-hour intravenous (IV) infusion every 2 weeks (see Section 5). Patients who develop disease progression on study treatment but who are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with single agent axitinib, avelumab, or avelumab combined with axitinib, 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 Pharmacokinetic Sample Collection Table. Pharmacokinetic samples for avelumab 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 up to approximately 8 additional patients to further evaluate the effect of avelumab on the PK of axitinib. Details are outlined in Section 7.2.

CCI [redacted]

25. **Mandatory Archival FFPE Tumor Tissue:** An archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from primary diagnosis specimen must be provided for all patients enrolled in the study and submitted to the Central Laboratory prior to enrollment. CCI [redacted] Cytology samples (eg FFPE cell pellet from Fine Needle Aspiration biopsy) are not acceptable. See Section 6.1.1 and Section 7.4.1.

26. **Mandatory Recent FFPE Tumor Tissue Block:** A baseline *de novo* tumor biopsy (biopsied tumor lesion should not be a RECIST target lesion) must be obtained for all patients enrolled in the study. CCI [redacted] For baseline *de novo* biopsy, tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. The *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. CCI [redacted] See Section 6.1.1 and Section 7.4.1.

27. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Cycle 1, 2, 3, 4, 6 and 8. Subsequently, testing should be performed approximately every 12 weeks until cycle 50. All samples should be drawn within 2 hours before start of avelumab infusion. Also see the Schedule for Pharmacokinetic Sample Collection Table. Additional samples for anti-avelumab antibodies (and simultaneous PK draws for measurement of avelumab) will be collected at the Day 30 Follow-up visit after the end of avelumab treatment. All the samples that are positive for ADA may also undergo characterization for Nab. See Section 7.3.

(X) = only if activity not performed in prior 3 days.

SCHEDULE OF ACTIVITIES for END OF TREATMENT and SHORT-/LONG-TERM FOLLOW-UP Periods
Patients participating in Dose Finding Phase and up to 8 additional patients enrolled for further PK assessment

Visit Identifiers[1]	End of Treatment/Withdrawal[2]	Post-Treatment Follow-Up	
		Short-Term Follow-Up (Day 30, Day 60, Day 90 [±3 days])[3]	Long-Term Follow-Up (±14 days)
Clinical Assessments			
Physical Examination[4]	X	X	
Contraception Check[5]	X	X (only at Fu Day 30)	
ECOG Performance Status	X	X	X
Vital Signs[6]	X	X	
Laboratory Studies			
Hematology[7]	X	X	
Blood Chemistry[7]	X	X	
Coagulation[7]	If clinically indicated		
Thyroid Function Tests[8]	X	X	
ACTH[9]	X	X	
HBV, HCV Tests	If clinically indicated		
Serum/Urine Pregnancy Test[10]	X	X	
Urinalysis[11]	X		
12-Lead ECG[12]	X		
Disease Assessments			
Tumor Assessments (including scans)[13]	Q6W after Cycle 1 Day 1 up to 1 year after the first dose; Q12W thereafter		
Survival[14]		X	X
Other Clinical Assessments			
Adverse Events[15]	X		
Concomitant Medications/Treatments[16]	X	X	
New Anticancer Therapy	X	X	X

Visit Identifiers[1]	End of Treatment/Withdrawal[2]	Post-Treatment Follow-Up	
		Short-Term Follow-Up (Day 30, Day 60, Day 90 [±3 days])[3]	Long-Term Follow-Up (±14 days)
Other Samplings			
Pharmacokinetics[17]		See SoA for PK	
[redacted] CCI [redacted]	[redacted]	[redacted]	
De Novo FFPE Tumor Tissue Block[19]	X		
Anti-Avelumab Antibodies and Neutralizing Antibodies[20]		See SoA for PK	

ACTH = adrenocorticotropic hormone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; Fu= follow-up; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetics; Q12W = every 12 weeks.

Footnotes for Schedule of Activities for END OF TREATMENT and SHORT-/LONG-TERM FOLLOW-UP Periods
Patients participating in Dose Finding Phase and up to 8 additional patients enrolled for further PK assessment

1. **Visit Identifiers:** Acceptable time windows for performing each assessment are described in the column headers.
2. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
3. **Short- and Long-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of investigational product or until the time of initiation of new anticancer treatment.
   Beyond the 90 days until the end of the study, all patients will be followed every 3 months (±14 days) for survival, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and new systemic anticancer treatment within the long-term follow-up.
4. **Physical Examination:** Includes an examination of major body systems and weight (height included at Screening only).
5. **Contraception Check:** Male patients with female partner of childbearing potential and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of1 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
6. **Vital Signs:** Vital signs to include: 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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit.
7. **Hematology, Blood Chemistry (Full Chemistry), and Coagulation**: Required tests are listed in Table 8. May also be performed when clinically indicated.
8. **Thyroid Function Tests:** free T4 and TSH will be performed at End of Treatment/Withdrawal and at the 30, 60, and 90 days Follow-up visits. Additional tests should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.

9. **ACTH**: ACTH tests will be performed at End of Treatment/Withdrawal and at the 30, 60, and 90 days Follow-up visits. Additional tests should be performed when clinically indicated. See Table 8.
10. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a pregnancy test (serum or urine) will be performed at the End of Treatment/Withdrawal visit and at the 30, 60, and 90 days Follow-up visits, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/(Ethics Committees (ECs) or if required by local regulations (see Section 7.1.1).
11. Urinalysis: Required only at End of Treatment. To be performed as clinically indicated at other time points. See Table 8.
12. **12-Lead Electrocardiogram (ECG)**: See Section 7.1.5 for details. ECG measurements will be obtained at End of Treatment/Withdrawal. Three consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood samples draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic adverse event (AE; eg, syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
13. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET, required at baseline then 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 complete response for patients who have bone metastases. See Section 7.6. The CT and MRI 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, at 6 weeks after the first dose of therapy (ie, Cycle 1 Day 1), then every 6 weeks up to 1 year from the first dose of therapy and every 12 weeks thereafter until confirmed disease progression regardless of initiation of subsequent anti-cancer therapy. Assessments will be performed according to calendar days, regardless of treatment delays or interruptions. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected progressive disease [PD], symptomatic deterioration, etc.). Complete response (CR) and partial response (PR) must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 CCI [redacted]). See Section 7.6 for additional information.
14. Survival: All patients will be followed for survival and subsequent anticancer therapies every 3 months (±14 days) until death, end of the study or patient withdrawal of consent, whichever comes first. For patients refusing to go back to the site a telephone contact is acceptable.

15. **Adverse Events:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Advers Events (CTCAE) version 4.03. For serious adverse events (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 study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occuring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the 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 1 dose of study treatment through and including 90 calendar days after the last of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.

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

17. **Pharmacokinetics**: Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic Sample Collection Table. Pharmacokinetic samples for avelumab 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 up to approximately 8 additional patients to further evaluate the effect of avelumab on the PK of axitinib. Details are outlined in Section 7.2.

CCI [redacted]

19. ***De Novo* FFPE Tumor Tissue Block:** A *de novo* (ie, fresh biopsy) tumor sample should be collected at the time of discontinuation of either drugs and at the End of Treatment/Withdrawal, unless clinically contraindicated. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. The *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded as per routine (see Study Manual), CCI [redacted] (see Section 6.1.1 for details) should be submitted to the Central Laboratory. See Section 6.1.1 and Section 7.4.1.

20. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies (and simultaneous PK draws for measurement of avelumab) will be collected at the Day 30 Follow-up visit after the end of avelumab treatment. All the samples that are positive for ADA may also undergo characterization for Nab. Also see the Schedule for Pharmacokinetic Sample Collection Table. See Section 7.3.

SCHEDULE OF ACTIVITIES for SCREENING and STUDY TREATMENT Periods
Patients participating in Dose Expansion Phase

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 14 days)			
		Cycle 1		Cycles ≥2 (until amend. #4 approval)	Cycles ≥2 (after amend. #4 approval)
	≤28 Days Prior to Enrollment or Randomization	Day 1	Day 8 (±1 day)	Day 1 (±3 days)	Day 1 (±3 days)
Clinical Assessments					
Informed Consent[2]	X				
Medical/Oncological History[3]	X				
Baseline Signs/Symptoms[4]		X			
Physical Examination[5]	X	X	X	X	X (Q6W)
Contraception Check[6]	X	X		X	X (Q6W)
ECOG Performance Status	X	X	X	X	X (Q6W)
Vital Signs[7]	X	X	X	X	X (Q6W)
Home Blood Pressure Monitoring[8]		X			
Laboratory Studies					
Hematology[9]	X	X	X	X	X (Q6W)
Blood Chemistry[9]	X	X[10]	X[10]	X[10]	X[10] (Q6W)
Coagulation[9]	X	X	X	X	If clinically indicated
Thyroid Function Tests[11]	X			X (Cycles 4, 7, 13 then Q12W)	
ACTH[12]	X			X (Cycle 6, then Q12W`)	
HBV, HCV Tests	X	If clinically indicated			
Serum/Urine Pregnancy Test[13]	X	X		X	
Urinalysis[14]	X	X		X (Cycle 3 then every odd cycle)	X (Q12W)
12-Lead ECG[15]	X	X		X (Cycle 4)	

Visit Identifiers[1]	**Screening**	**Study Treatment (1 cycle = 14 days)**			
		Cycle 1		**Cycles ≥2 (until amend. #4 approval)**	**Cycles ≥2 (after amend. #4 approval)**
	≤28 Days Prior to Enrollment or Randomization	**Day 1**	**Day 8 (±1 day)**	**Day 1 (±3 days)**	**Day 1 (±3 days)**
Disease Assessments					
Tumor Assessments (including scans)[16]	X	Q6W after Cycle 1 Day 1 up to 1 year after the[t] first dose; Q12W thereafter			
Other Clinical Assessments					
Follow-up for Axitinib Dosing Compliance[17]		X (D5 ± 3 days)		X[17](D5 ± 3 days)	
Adverse Events[18]		X			
Concomitant Medications/Treatments[19]	X	X	X	X	X
Enrollment by Study Treatment[20]					
Avelumab[21]		X[21]		X[21]	
Axitinib[21]		X			
Other Samplings					
Pharmacokinetics[22]		X	X	X (Cycles 2, 3, 4, 6, 8, then Q12W until cycle 50)	
[redacted] CCI	[redacted]	[redacted]		[redacted]	
Mandatory Archival FFPE Tumor Tissue[24]	X				
Mandatory Recent *De Novo FFPE* Tumor Block[25]	X				
Anti-Avelumab Antibodies and Neutralizing Antibodies[26]		X		X (Cycles 2, 3, 4, 6, 8, then Q12W until cycle 50)	

ACTH=adrenocorticotropic hormone; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed and paraffin-embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; PK=pharmacokinetics; Q6W= every 6 weeks; Q12W=every 12 weeks.

Footnotes for Schedule of Activities for SCREENING and STUDY TREATMENT Periods
Patients participating in Dose Expansion Phase

1. **Visit Identifiers:** All assessments should be performed prior to the start of study treatment unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.

3.	**Medical/Oncological History:** To include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery, and radiation therapy.
4.	**Baseline Signs/Symptoms:** To be recorded predose for all patients on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment.
5.	**Physical Examination:** Includes an examination of major body systems and weight (height included at Screening only).
6.	**Contraception Check:** Male patients with female partner of childbearing potential and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
7.	**Vital Signs:** Vital signs to include: 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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit. After amendment #4 approval, required every 6 weeks.
8.	**Home Blood Pressure Monitoring:** All patients will receive home blood pressure monitoring devices and blood pressure will be monitored at home. 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 disturbances), although a different blood pressure threshold for contacting the site may be used according to the investigator's clinical judgment (see Section 5.3.5.2).
9.	**Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 8. May also be performed when clinically indicated.
10.	**Blood Chemistry:** Full chemistry panel (required tests are listed in Table 8) is required as follows: at Screening, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks thereafter. Core chemistry panel (required tests are listed in Table 8) is required as follows: Cycle 1 Day 8, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 2 weeks thereafter. If full and core chemistry panels are scheduled at the same visit, only the full chemistry panel will be performed. After amendment #4 approval required every 6 weeks. Required tests are listed in Table 8.
11.	**Thyroid Function Tests:** Free T4 and TSH will be performed at Screening, Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 13, Day 1, and then Q12W thereafter. Additional tests should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.
12.	**ACTH**: ACTH tests will be performed at Screening, Cycle 6 Day 1, then Q12W thereafter. Additional tests should be performed when clinically indicated. See Table 8.
13.	**Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at two occasions prior to starting combination study treatment: once at the start of screening and at the Cycle 1 Day 1 visit immediately before the administration of avelumab in combination with axitinib. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle during the active treatment period, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRB)/Ethics Committees (ECs) or if required by local regulations (see Section 7.1.1).
14.	**Urinalysis**: Required at Screening, at Cycle 1 Day 1 and then at Day 1 of every odd cycle and at the End of Treatment. After amendment #4 approval required every 12 weeks. If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein will have to be quantified by 24-hour urine collection. To be performed as clinically indicated at other time points. See Table 8.

15. **12-Lead Electrocardiogram (ECG):** See Section 7.1.5 for details. All ECG measurements will be obtained at Screening, Cycle 1 Day 1, and Cycle 4 Day 1. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). Triplicate ECGs at Cycle 4 Day 1 will be collected pre-dose and at 2 hours post-axitinib dosing. Triplicate ECGs at Cycle 1 Day 1 will be prior to avelumab infusion and within 30 minutes post end of infusion. When coinciding with blood samples draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic adverse event (AE; eg, syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

16. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET, required at baseline then 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 complete response for patients who have bone metastases. See Section 7.6. The CT and MRI 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, at 6 weeks after the first dose of therapy (ie, Cycle 1 Day 1), then every 6 weeks up to 1 year from the first dose of therapy and every 12 weeks thereafter until confirmed disease progression regardless of initiation of subsequent anti-cancer therapy. Assessments will be performed according to calendar days, regardless of treatment delays or interruptions. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected progressive disease [PD], symptomatic deterioration, etc.). Complete response (CR) and partial response (PR) must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 CCI [redacted]). See Section 7.6 for additional information.

17. **Follow-up for Axitinib Dosing Compliance:** Follow-up by telephone will be done to confirm patient understanding and compliance with dosing instructions on Cycle 1 Day 5. Axitinib dosing compliance will also be assessed following any dose modification. If needed, patients will be retrained.

18. **Adverse Events:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. After amendment #4 approval, patients receiving axitinib single agent will visit the site every 6 weeks. Between site visits, AEs collection will be performed every 2 weeks by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. For serious adverse events (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 study treatment, through and including 90 calendar days after the last administration of study treatment. SAEs occuring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the 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 1 dose of study treatment through and including 90 calendar days after the last of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.

19. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). After amendment #4 approval, patients receiving axitinib single agent will visit the site every 6 weeks. Between site visits, concomitant medication collection will be performed every 2 weeks by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.
20. **Enrollment:** Patient number and dose level allocation will be operated by the sponsor (see Section 5.1). Required information: site and patient identifiers and demographic information. Study treatment (avelumab in combination with axitinib) should begin within 3 days of registration/randomization.
21. **Study Treatment:** Axitinib will be given orally (PO) twice daily (BID) on a continuous schedule. Avelumab will be given as a 1-hour intravenous (IV) infusion every 2 weeks (see Section 5). Patients who develop disease progression on study treatment but who are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with single agent axitinib, avelumab, or avelumab combined with axitinib, provided that the treating physician has determined that the benefit/risk for doing so is favorable.
22. **Pharmacokinetics**: Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic Sample Collection Table. Pharmacokinetic samples for avelumab will be collected from all patients in the study. Details are outlined in Section 7.2.

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24. **Mandatory Archival FFPE Tumor Tissue:** An archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from primary diagnosis specimen must be provided for all patients enrolled in the study and submitted to the Central Laboratory prior to enrollment. CCI [redacted] Cytology samples (eg, FFPE cell pellet from Fine Needle Aspiration biopsy) are not acceptable. See Section 6.1.1 and Section 7.4.1.
25. **Mandatory Recent *De Novo* FFPE Tumor Tissue Block:** A baseline *de novo* tumor biopsy (biopsied tumor lesion should not be a RECIST target lesion) must be obtained for all patients enrolled in the study. CCI [redacted] The *de novo* biopsy should be formalin-fixed and paraffin-embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. CCI [redacted] See Section 6.1.1 and Section 7.4.1.
26. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Cycle 1, 2, 3, 4, 6, and 8. Subsequently, testing should be performed approximately every 12 weeks until cycle 50. All samples should be drawn within 2 hours before start of avelumab infusion. Also see the Schedule for Pharmacokinetic Sample Collection Table. All the samples that are positive for ADA may also undergo characterization for Nab. See Section 7.3.

SCHEDULE OF ACTIVITIES for END OF TREATMENT and SHORT-/LONG-TERM FOLLOW-UP Periods
Patients participating in Dose Expansion Phase

Visit Identifiers[1]	End of Treatment /Withdrawal[2]	Post-Treatment Follow-Up	
		Short-Term Follow-Up (Day 30, Day 60, Day 90 [[±3 days])[3]	Long-Term Follow-Up (±14 days)[3]
Clinical Assessments			
Physical Examination[4]	X	X	
Contraception Check[5]	X	X (only at Fu Day 30)	
ECOG Performance Status	X	X	X
Vital Signs[6]	X	X	
Laboratory Studies			
Hematology[7]	X	X	
Blood Chemistry[7]	X	X	
Coagulation[7]	if clinically indicated		
Thyroid Function Tests[8]	X	X	
ACTH[9]	X	X	
HBV, HCV testing	if clinically indicated		
Serum/Urine Pregnancy Test[10]	X	X	
Urinalysis[11]	X		
12-Lead ECG[12]	X		
Disease Assessments			
Tumor Assessments (including scans)[13]	Q6W after Cycle 1 Day 1 up to 1 year after the first dose; Q12W thereafter		
Survival[14]		X	X
Other Clinical Assessments			
Adverse Events[15]	X		
Concomitant Medications/Treatments[16]	X	X	
New Anticancer Therapy	X	X	X
Other Samplings			
Pharmacokinetics[17]		See SoA for PK	
CCI [redacted]			

Visit Identifiers[1]	End of Treatment /Withdrawal[2]	Post-Treatment Follow-Up	
		Short-Term Follow-Up (Day 30, Day 60, Day 90 [[±3 days])[3]	Long-Term Follow-Up (±14 days)[3]
De Novo FFPE Tumor Block[19]	X		
Anti-Avelumab Antibodies and Neutralizing Antibodies[20]		See SoA for PK	

ACTH=adrenocorticotropic hormone; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed and paraffin-embedded; Fu= follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; PK=pharmacokinetics; Q12W=every 12 weeks.

Footnotes for Schedule of Activities for END OF TREATMENT and SHORT-/LONG-TERM FOLLOW-UP Periods **Patients participating in Dose Expansion Phase**
1. **Visit Identifiers:** Acceptable time windows for performing each assessment are described in the column headers.
2. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
3. **Short- and Long-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of investigational product or until the time of initiation of new anticancer treatment. Beyond the 90 days until the end of the study, all patients will be followed every 3 months (±14 days) for survival, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and new systemic anticancer treatment within the long-term follow-up.
4. **Physical Examination:** Includes an examination of major body systems and weight (height included at Screening only).
5. Contraception Check: Male patients with female partner of childbearing potential and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
6. **Vital Signs:** Vital signs to include: 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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit.
7. **Hematology, Blood Chemistry (Full Chemistry), and Coagulation**: Required tests are listed in Table 8. May also be performed when clinically indicated.
8. **Thyroid Function Tests:** Free T4 and TSH will be performed at End of Treatment/Withdrawal and at the 30, 60, and 90 day Follow-up visits. Additional tests should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 8.
9. **ACTH**: ACTH tests will be performed at End of Treatment/Withdrawal and at the 30, 60, and 90 day Follow-up visits. Additional tests should be performed when clinically indicated. See Table 8.

10. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a pregnancy test (serum or urine) will be repeated at the End of Treatment/Withdrawal visit and at the 30, 60, and 90 day Follow-up visits, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations (see Section 7.1.1).

11. Urinalysis: Required only at End of Treatment. To be performed as clinically indicated at other time points. See Table 8.

12. **12-Lead Electrocardiogram (ECG)**: See Section 7.1.5 for details. ECG measurements will be obtained at End of Treatment/Withdrawal. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When coinciding with blood samples draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic adverse event (AE; eg, syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

13. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET, required at baseline then 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 complete response for patients who have bone metastases. See Section 7.6. The CT and MRI 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, at 6 weeks after the first dose of therapy (ie, Cycle 1 Day 1), then every 6 weeks up to 1 year from the first dose of therapy and every 12 weeks thereafter until confirmed disease progression regardless of initiation of subsequent anti-cancer therapy. Assessments will be performed according to calendar days, regardless of treatment delays or interruptions. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected progressive disease [PD], symptomatic deterioration, etc.). Complete response (CR) and partial response (PR) must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 CCI [redacted]). See Section 7.6 for additional information.

14. Survival: All patients will be followed for survival and subsequent anticancer therapies every 3 months (±14 days) until death, end of the study or patient withdrawal of consent, whichever comes first. For patients refusing to go back to the site a telephone contact is acceptable.

15. **Adverse Events:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Advers Events (CTCAE) version 4.03. For serious adverse events (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 study treatment, through and including 90 calendar days after the last dose of study treatment. SAEs occuring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the 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 1 dose of study treatment through and including 90 calendar days after the last dose of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.

16. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
17. **Pharmacokinetics**: Samples will be collected at the time points indicated in the Schedule for Pharmacokinetic Sample Collection Table. Pharmacokinetic samples for avelumab will be collected from all patients in the study. Details are outlined in Section 7.2.
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19. ***De Novo* FFPE Tumor Tissue Block:** A *de novo* (ie,, fresh biopsy) tumor sample should be collected at the time of discontinuation of either drugs and at the End of Treatment/Withdrawal, unless clinically contraindicated. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. The *de novo* biopsy(ies) should be formalin-fixed and paraffin-embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) or slides if blocks cannot be provided (see Section 6.1.1 for details) should be submitted to the Central Laboratory. See Section 6.1.1 and Section 7.4.1.
20. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** One blood sample (3.5 mL) for anti-avelumab antibodies (and simultaneous PK draws for measurement of avelumab) will be collected at the Day 30 Follow-up visit after the end of avelumab treatment. All the samples that are positive for ADA may also undergo characterization for Nab. Also see the Schedule for Pharmacokinetic Sample Collection Table. See Section 7.3.

SCHEDULE FOR PHARMACOKINETIC SAMPLE COLLECTION

Pharmacokinetic samples are to be obtained on the same day as all other scheduled assessments outlined in the Schedule of Activities table.

Protocol Activity	**Axitinib**							**Avelumab in Combination with Axitinib**													
								Cycle 1			**Cycles 2 and 3**	**Cycle 4**							**Cycle 6**	**Cycle 8 and Every 12 weeks Thereater until cycle 50**	**Day 30 Follow-Up**
	Lead-in Day 7							**Day 1**		**Day 8 (±1 day)**	**Day 1 (±3 days)**	**Day 1 (±3 days)**							**Day 1 (±3 days)**	**Day 1 (±3 days)**	
Hours post dose	0[f]	1	2	3	4	6	8	0[f]	1	168	0[f]	0[f]	1	2	3	4	6	8	0[f]	0[f]	
PK for axitinib[a]	x	x	x	x	x	x	x					x	x	x	x	x	x	x			
PK for avelumab[b]								x	x[d]	x[e]	X	x	x[d]						x	x	x
ADAs[c]								x			X	x							x	x	x

PK=pharmacokinetics; ADAs=anti-drug antibodies
Note that PK samples for avelumab and anti-avelumab-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 up to approximately 8 additional patients enrolled to assess the effect of avelumab on the PK of axitinib.

a. One sample (3 mL) collected at each time point for axitinib.
b. One sample (3.5 mL) collected at each time point for avelumab. An additional PK samples will be collected at the Day 30 Follow-up visit after the end of avelumab treatment.
c. One sample (3.5 mL) collected at each time point for anti-avelumab antibodies. An additional anti-avelumab antibody samples will be collected at the Day 30 Follow-up visit after the end of avelumab treatment.
d. Sample may be collected within 30 minutes after end of avelumab infusion.
e. Sample may be collected at any time between Cycle 1 Day 7 and Cycle 1 Day 9 for avelumab; the exact time/day of collection is to be recorded on the case report form (CRF).
f. Pre-dose sample.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Previously untreated advanced renal cell carcinoma (aRCC).

The mechanisms of action of avelumab and axitinib are described in Sections 1.2.2.1 and 1.2.2.2, respectively.

1.2. Background and Rationale

1.2.1. Renal Cell Cancer

Renal cell carcinoma (RCC) is the most common kidney cancer and constitutes about 3% of all malignant tumors in adults.[1] RCC is often first detected at an advanced stage, with 25-30% of patients having metastatic disease at diagnosis.

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 (Types I and II), chromophobe, collecting duct, and unclassified RCC.[2] 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 vascular endothelial growth factor [VEGF] and platelet-derived growth factor [PDGF]) which induce tumorigenesis. Clear cell RCC is a highly vascular tumor with high expression of VEGF, VEGF receptor (VEGFR), and PDGF receptor (PDGFR).[3]

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.[4]

There are 7 molecularly targeted agents approved in the United States (US) as systemic therapy for advanced RCC that is predominantly clear cell. First line systemic therapy is usually one of the VEGFR tyrosine kinase inhibitors (TKIs) (sunitinib, pazopanib, or sorafenib), the monoclonal anti-VEGF antibody bevacizumab (given in combination with interferon [IFN]-α) or the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus. These drugs are used sequentially as single agents in subsequent lines of therapy for advanced clear cell RCC.[4-7]

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

The first investigational product in the present clinical trial is avelumab (MSB0010718C), a fully human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype. Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody MSB0010718C.

Avelumab selectively binds to programmed death-ligand 1 (PD-L1) and competitively blocks its interaction with programmed death protein-1 (PD-1). Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore, is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death-ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[8] For complete details of the in vitro and nonclinical studies, refer to the avelumab investigator's brochure.[9]

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, and Hodgkin's Lymphoma, as a single agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

As of 05 November 2015, more than 1400 patients have been treated with avelumab. The largest trial is study EMR100070-001, a Phase 1, open-label, multiple ascending-dose clinical study aimed to investigate the safety, tolerability, pharmacokinetics (PK), biological activity, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. Study EMR100070 001 consists of 2 parts, a dose-escalation phase and a dose-expansion phase, the latter performed in selected tumor indications. Avelumab is administered intravenously (IV) at the assigned dose level as a 1-hour infusion once every 2 weeks (Q2W).

As of 05 November 2015, a total of 53 patients were treated in the dose-escalation phase of Trial EMR10070-001, with 4, 13, 15, and 21 patients being treated with avelumab of 1, 3, 10, and 20 mg/kg, respectively. None of the patients treated with doses up to 10 mg/kg experienced a dose-limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well-tolerated dose for further investigation in the dose-expansion cohorts. One DLT (a Grade 3 immune-related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the 20 mg/kg dose level.

As of 05 November 2015, 1300 patients have been enrolled in the tumor type specific expansion cohorts of study EMR 100070-001 and treated with the recommended dose of 10 mg/kg avelumab Q2W. A summary of the safety data for the pooled expansion cohort is provided here.

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Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab investigator's brochure. The reference safety information (RSI) can be found in tabular format in Section 6.2 of the avelumab IB (Investigator Brochure).[9]

1.2.2.2. Axitinib (INLYTA®, AG-013736)

The other investigational product in the present clinical trial is axitinib (INLYTA®, AG-013736), an oral, small molecule, TKI selective for VEGFRs 1, 2, and 3, approved multinationally for the treatment of advanced RCC (aRCC) after failure of one prior systemic therapy (actual indication varies according to region/country).[10]

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 juxtamembrane domain containing human VEGFR 2 recombinant protein.[11] In additional kinase assays, axitinib showed potent and ATP-competitive inhibition of the VEGFRs 1, 2, and 3 and PDGFR-β, but not other closely

related family kinases. Receptor binding studies and cell-based assays confirmed that axitinib is a potent and selective inhibitor of VEGFRs 1, 2, and 3. Axitinib was shown to have antiangiogenic activity in a number of models including spontaneous pancreatic islet-cell tumors of RIP-TAG-2 transgenic mice model and demonstrated antitumor efficacy including marked cytoreductive antitumor activity in multiple tumor models implanted in athymic mice.

The safety and efficacy of axitinib were evaluated in a randomized, open-label, multicenter Phase 3 study. Patients with aRCC (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 progression-free survival (PFS) endpoint, 6.7 months (95% confidence interval [CI]: 6.3, 8.6) vs 4.7 months (95% CI: 4.6, 5.6), respectively (hazard ratio 0.665; 95% CI 0.544-0.812; one sided p <0.0001). There was no statistically significant difference between the treatment arms in the secondary overall survival (OS) endpoint, 20.1 months (95% CI: 16.7, 23.4) vs 19.2 months (95% CI: 17.5, 22.3) for axitinib and sorafenib (hazard ratio 0.969, 95% CI 0.800-1.174; one sided p=0.3744), 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.[12]

In another 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) as assessed by Independent Review Committee, respectively, with stratified hazard ratio 0.77 (95% CI: 0.56, 1.05; one sided p=0.038). The axitinib ORR assessed by an Independent Radiology Review Committee was 32%, risk ratio 2.21, (95% CI: 1.31, 3.75, stratified one-sided p=0.0006). Adverse events more common (≥10%) with axitinib versus sorafenib were diarrhoea, hypertension, weight decrease, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain; those more common with sorafenib versus axitinib included palmar-plantar erythrodysesthesia (hand-foot) syndrome and rash, alopecia and erythema.[13] Toxicities in this clinical trial were generally tolerable and manageable and similar to those observed in clinical trials of axitinib in pre-treated aRCC patients.[13]

Overall, the adverse events reported for axitinib in clinical studies were considered generally tolerable and manageable. For single-agent axitinib, the most common adverse events (>20% of patients) reported from 1445 cancer patients regardless of causality included diarrhea, hypertension, decrease appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia syndrome, hypothyroidism, and proteinuria. Grade ≥3 events that occurred most frequently were hypertension, fatigue, and diarrhea.[11]

Following oral administration, axitinib is rapidly absorbed (median T_{max} 2.5-4.1 hours). The plasma half life of axitinib ranges from 2.5 to 6.1 hours and steady-state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4-fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear PK within the 1-mg to 20-mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%. Axitinib may be administered with or without food. Axitinib is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1. The predominant sulfoxide and N-glucuronide metabolites in human plasma show approximately ≥400-fold less in vitro potency against VEGFR-2 compared to axitinib.

Complete information for axitinib may be found in the SRSD, which for this study is the axitinib investigator's brochure. The RSI can be found in tabular format in Section 7.8 of the axitinib IB.[11]

1.2.3. Rationale for Studying Avelumab in Combination with Axitinib 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 pathway inhibitors have been approved in a number of indications, including the treatment of aRCC.[14,15]

Until 2005, IFN-α and high-dose interleukin (IL)-2 therapies were the standards of care for patients with aRCC, albeit with modest efficacy. Since then, development and approval of multiple VEGF pathway and mTOR inhibitors have significantly improved the outcomes of aRCC patients. These agents include the VEGFR TKIs sunitinib, pazopanib, axitinib and sorafenib; the mTOR inhibitors temsirolimus and everolimus; and the anti-VEGF monoclonal antibody bevacizumab. However, durable and complete responses in aRCC patients are uncommon; the majority of patients will eventually develop resistance, exhibit disease progression while on therapy, and succumb to death due to metastatic disease. Response rates for previously treated aRCC patients are in the 15-25% range, and median survival after diagnosis is under 1 year.[1]

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.[16] These reports have generated considerable interest in immunotherapeutic approaches in the treatment of aRCC patients, especially with advent of immune checkpoint inhibitors such as anti-PD-1 and

anti-PD-L1 antibodies in recent years. Upregulation of PD-1 receptor on tumor-infiltrating lymphocytes (TILs), and its ligand PD-L1 on tumors, are associated with more aggressive disease and poor prognosis.[17,18]

Monoclonal antibodies (mAb) that block the PD-1/PD-L1 interaction are novel immunotherapeutic approaches for aRCC, which have shown single-agent efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy.[19,20] Nivolumab, a high-affinity, fully human anti-PD-1 mAb has shown durable tumor response with ORR of about 20% and median PFS of about 16 weeks in heavily pretreated aRCC patients.[21,22] When nivolumab was combined with a VEGF TKI (sunitinib or pazopanib), it demonstrated more pronounced anti-tumor response. Amin et al reported the data from combinations of sunitinib or pazopanib with nivolumab at the American Society of Clinical Oncology (ASCO) 2014 annual meeting.[23] The pazopanib plus nivolumab arm was discontinued due to early safety issues; however, sunitinib (50 mg, 4 weeks on/2 weeks off) was successfully combined with nivolumab 5 mg/kg every 3 weeks (Q3W), and dose expansion was subsequently completed in previously untreated aRCC patients. ORR was 52% (17/33) for nivolumab in combination with sunitinib, and 45% (9/20) for nivolumab in combination with pazopanib. Median duration of response (DR) was 37.1 weeks (95% CI: 18.1-80.0+), and median PFS was 48.9 weeks (95% CI: 41.6-66.0) with sunitinib plus nivolumab. MPDL3280A, another human mAb that targets PD-L1, has shown ORR of 13% and stable disease (SD) ≥24 weeks in 32% of patients with previously treated RCC when administered as a single agent. Results from the combination of bevacizumab 15 mg/kg Q3W with MPDL3280A (20 mg/kg) were presented by McDermott et al at the European Society for Medical Oncology (ESMO) 2014 annual meeting.[24] Data were limited, but in previously untreated aRCC patients, there were 4 of 10 (40%) patients who had partial responses (PRs). Five additional patients had a best response of SD, and almost all (9 out of 10) responding patients were still on treatment at the time of analysis. These data, although preliminary, demonstrate the benefit of combining an anti-PD-1 or PD-L1 antibody with an anti-VEGF pathway agent in aRCC patients.

The combination of nivolumab with ipilimumab, a fully human monoclonal antibody to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed acceptable safety and encouraging antitumor activity in patients with metastatic RCC. Patients were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (Arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (Arm N1 + I3) IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity. Confirmed objective response (OR) was observed in 9/21 patients in arm N3 + I1 and in 11/23 patients in Arm N1 + I3. The median PFS was 36.6 weeks and 38.3 weeks in Arm N3 + I1 and in Arm N1 + I3, respectively.[25] Antitumor activity of single-agent axitinib 5 mg BID in previously untreated 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 PFS between patients treated with axitinib or sorafenib, axitinib was associated with a longer median PFS time (mPFS 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 those demonstrated earlier in Phase 3 clinical trials of other approved VEGFR TKIs in the first-line treatment of aRCC patients.[13] Toxicities in

this clinical trial were generally tolerable and manageable, and similar to those observed in clinical trials with axitinib in pre-treated aRCC patients.[12]

Avelumab (MSB0010718C) is a fully human monoclonal antibody (mAb) of the IgG1 isotype that specifically targets and blocks PD-L1 (see Section 1.2.2.1).[26] Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody MSB0010718C.

As to the safety profile of avelumab see Section 1.2.2.1.

Currently, the 10 mg/kg dose is the recommended Phase 2 dose for avelumab in single-agent studies. In the dose escalation study of avelumab, the 10 mg/kg dose was found to be well-tolerated and did not result in any DLT. In addition, all patients treated at this dose had a median trough concentration >1 μg/mL, the necessary concentration for >95% TO. Therefore, the lower 5 mg/kg dose is expected to be well-tolerated and based upon pharmacokinetic modeling and the dose-linear PK characteristics of avelumab, median trough concentrations should achieve 95% TO in all patients.

The risk of hepatotoxicity is low in aRCC patients on axitinib, with an overall rate of Grade 3/4 ALT or AST increased <0.6% for each.[27] The incidence of hematological toxicity was also low for axitinib in this patient population (eg, Grade 3/4 platelet count decreased and neutrophil count decreased 0.3% for each).[27]

Preliminary Safety Data of Avelumab as Monotherapy in aRCC.

In the aRCC cohort of the Phase 1 study EMR 100070-001, 18 patients with aRCC in the second-line and beyond treatment setting received avelumab IV Q2W at the dose of 10 mg/kg (see Section 1.2.2.1).[9] Current data indicate that the safety profile of the aRCC cohort is consistent with that of the overall population of study EMR 100070-001. Since December 2015, an additional cohort of approximately 30 patients with aRCC in the first-line treatment setting has started enrollment within the EMR 100070-001 study.

Safety Considerations for Avelumab in Combination with Axitinib

The combination of avelumab with axitinib has not been previously studied in patients; therefore, there are currently no safety data from this combination. There are no expected overlapping toxicities between avelumab and axitinib, except for fatigue, nausea/diarrhea, and hypothyroidism, which are usually low-grade events easily manageable following the adverse event management guidelines implemented in the study protocol. Additional safety concerns are not expected from combining avelumab with axitinib given their distinct mechanisms of action and toxicity profiles.

Overall, the observed benefit-risk profile supports the further investigation of avelumab in combination with axitinib in the patient population chosen for this study.

It is proposed that the addition of the PD-L1 inhibitor, avelumab, to the VEGF pathway inhibitor, axitinib, may provide additional clinical benefit compared to treatment with an anti-VEGFR TKI alone without unacceptable toxicity in untreated aRCC patients leveraging their complementary mechanisms of action. This study, therefore, is designed to determine

the recommended doses and provide the safety, PK, and preliminary efficacy of this combination regimen needed to support a subsequent randomized clinical trial of avelumab in combination with axitinib versus VEGFR TKI in the first-line aRCC treatment setting.

1.2.4. Rationale for Avelumab and Axitinib Starting Doses

1.2.4.1. Axitinib Starting Dose and Regimen

In this clinical trial, the axitinib starting dose will be 5 mg administered orally (PO) twice daily (BID) with or without food. This dose has proven to be safe and efficacious in aRCC and has been approved by regulatory authorities worldwide.

1.2.4.2. Avelumab Starting Dose and Regimen

In this clinical trial, the avelumab starting dose will be 10 mg/kg administered as 1-hour intravenous (IV) infusion every 2 weeks (Q2W). This dose is the recommended dose administered to a total of 480 patients in the ongoing dose-expansion phase of study EMR 100070-001 (see Section 1.2.2.1 for details).

1.3. Summary of Benefit Risk Assessment

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

Based on the nonclinical and Phase 1 clinical data available to date, the conduct of the trial with the proposed avelumab dose and regimen is considered justifiable.

As noted above (Section 1.2.3), blocking the PD-1/PD-L1 pathway by agents binding either PD-1 or PD-L1 (anti-PD-1 mAb or anti-PD-L1 mAb) is a novel immunotherapeutic approach for aRCC, and anti-PD-1 and anti-PD-L1 agents have shown single-agent efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy. Furthermore, anti-PD-1/PD-L1 antibodies have shown to produce objective response rates of 13% to 52% as single agents or in combination with a VEGF pathway inhibitor in patients with aRCC.[19,20,23] Recent studies suggested that TKI administration induces PD-L1 expression which might lead to immune tolerance and acquired resistance to VEGF targeted agents such as axitinib. Therefore, the addition of axitinib, which is a standard therapy for patients with RCC, might be synergistic with avelumab in treating patients with aRCC.

For single-agent avelumab, based on the nonclinical and Phase 1 trial EMR 100070-001 clinical data available to date, the conduct of the trial with the proposed avelumab dosing regimen is considered justifiable. The clinical safety data available to date, with single-agent avelumab in patients with advanced solid tumors, suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol.

Axitinib is approved multinationally for the treatment of aRCC after failure of one prior systemic therapy. Furthermore, axitinib has been studied as first-line aRCC treatment in a Phase 3 clinical trial, and in this treatment setting, the safety profile is comparable to the one observed in the second-line treatment setting.[12,13] Overall, the adverse events reported for axitinib in clinical studies is considered generally tolerable and manageable, and are well characterized (see Section 1.2.2.2).

The combination of avelumab with axitinib has not been previously studied in patients; therefore, there are currently no safety data for the combination. There are no expected overlapping toxicities between avelumab and axitinib, except for fatigue, nausea/diarrhea, and hypothyroidism, which are usually low-grade events easily manageable with symptomatic or steroid therapies and following the adverse event management guidelines implemented in the study protocol. Additional safety concerns are not expected from combining avelumab with axitinib given their distinct mechanisms of action and toxicity profiles.

These results, together with the acceptable safety profile of avelumab as currently demonstrated by the ongoing Phase 1 trial EMR100070-001, support the hypothesis that avelumab in combination with axitinib may represent an important therapeutic approach in patients with aRCC. Thus, the projected benefit/risk of avelumab given in combination with axitinib is favorable for investigation in this advanced cancer patient population.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To assess the safety and tolerability of avelumab in combination with axitinib 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 avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To assess the preliminary anti-tumor activity of avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To evaluate the OS of avelumab in combination with axitinib in patients with previously untreated advanced RCC.
- To characterize the PK of avelumab and axitinib when administered in combination, and to assess the effect of avelumab on the PK of axitinib.

- To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib.

- To assess the immunogenicity of avelumab when combined with axitinib.

CCI [redacted]

- CCI [redacted]

- CCI [redacted]

2.2. Endpoints

Primary Endpoint

- DLTs within the first 4 weeks (2 cycles) of treatment with avelumab in combination with axitinib.

Secondary Endpoints

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 4).
- Vital signs (blood pressure, pulse rate).
- Objective Response (OR) and Disease Control (DC) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix 2).
- Time-to-event endpoints: Duration of Response (DR), Progression-Free Survival (PFS), and Time to Tumor Response (TTR).
- Overall Survival (OS).
- PK parameters including C_{max}, T_{max}, AUC_{tau}, and $t_{1/2}$ as appropriate for axitinib; C_{trough} and C_{max} for avelumab.
- Tumor tissue biomarker status (ie, positive or negative based on, for example, PD-L1 expression and/or quantitation of tumor-infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry [IHC]).
- Anti-drug antibodies (ADAs; neutralizing antibodies [Nabs]) of avelumab when combined with axitinib.

CCI [redacted]

- CCI [redacted]
- CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b, open-label, multi-center, multiple-dose, safety, PK and pharmacodynamic study of avelumab in combination with axitinib in adult patients with previously untreated aRCC. This clinical study will be composed of a Dose Finding Phase and a Dose Expansion Phase.

The Dose Finding Phase will estimate the MTD and RP2D in patients with aRCC with clear cell histology who did not receive prior systemic therapy for advanced disease, using the modified toxicity probability interval (mTPI) method.[29] Dose finding will follow an mTPI design, with up to 3 potential dose levels (DL) to be tested:

- (DL1) avelumab 10 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1A) avelumab 5 mg/kg Q2W + axitinib 5 mg BID.
- (DL-1B) avelumab 10 mg/kg Q2W + axitinib 3 mg BID.

DL-1A and DL-1B will be explored concurrently in a randomized fashion only if the MTD is exceeded in DL1.

To understand the extent of any effects of avelumab on axitinib PK, 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 of the study. Since avelumab has a half-life of 3-5 days, it would not be feasible to run a lead-in with avelumab alone to study the PK of avelumab alone. Therefore, the effect of axitinib on avelumab will be evaluated by comparing avelumab trough concentrations at steady state in the presence of axitinib with those reported for avelumab alone in prior studies.

The Dose Finding Phase will lead to the identification of an Expansion Test Dose for avelumab in combination with axitinib in patients with aRCC who did not receive prior systemic therapy for their advanced disease. The Expansion Test Dose will either be the MTD (ie, the highest dose of avelumab and axitinib 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 avelumab in combination with axitinib will be evaluated in up to approximately 40 patients with previously untreated aRCC.

Based on the emerging PK data and after the completion of the dose-finding part of the study based on mTPI method, it may be necessary to enroll up to approximately 8 additional patients to further assess the effect of avelumab on the PK of axitinib. These additional patients will undergo the same evaluations and procedures as those described in the Schedule of Activities table for the Dose Finding Phase of the study and will be treated concurrently with the initiation of the Dose Expansion Phase of the study. With the exception of the mTPI-related assessments leading to determination of MTD, any other assessments or procedures described for the Dose Finding Phase will also apply to these additional patients.

Throughout the course of the study, patient safety will be closely monitored by the sponsor's study team. The number of patients to be enrolled in the Dose Finding Phase will depend on the observed safety profile, and the number of tested dose levels.

All patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy. Patients who do not return to the site should be contacted by telephone every 3 months as an alternative.

Study Treatment:

Axitinib will be given orally (PO) twice daily (BID), with or without food, on a continuous dosing schedule. Avelumab will be given as a 1-hour IV infusion Q2W. All patients will continue treatment with study drugs until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.4).

Patients will be monitored closely for toxicity, and in the event of significant toxicity, dosing of one or both drugs may be modified. Specifically, avelumab doses may be omitted or permanently discontinued, and axitinib doses may be delayed, reduced, or permanently discontinued, as per Section 5.3.5. 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 5.3.5.3). Avelumab treatment modification for drug-related toxicities, including immune-related adverse events (irAEs) and infusion-related AEs is described in Section 5.3.5.

In the Dose Finding Phase, intrapatient axitinib dose escalation is not permitted, except for patients treated at DL-1B. In these patients, after the completion of the primary DLT observation period, intrapatient axitinib dose escalation may occur according to the criteria described in Section 5.3.5.1. In the Dose Expansion Phase, intrapatient axitinib dose escalation may occur if the intrapatient escalation criteria are met (see Section 5.3.5.1).

Patients who stop one of the two study drugs (avelumab or axitinib) for reasons other than confirmed disease progression may continue on single-agent treatment with the other drug until disease progression (RECIST v.1.1), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is prematurely terminated by the sponsor, whichever comes first. Patients who are still deriving clinical benefit following continued treatment for more than 2 years will be provided an option for continued study treatment (eg, a rollover study).

Patients who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression thereafter will be eligible for re-treatment with avelumab at the discretion of the investigator and after discussion with the sponsor's medical monitor if 1) no cancer treatment was administered other than axitinib since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, and 3) the trial is still open. Patients will resume avelumab therapy at the same dose and schedule applied at the time of discontinuation.

Patients who develop disease progression on study treatment but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab combined with axitinib, single-agent avelumab, or single-agent axitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Tumor Assessment: Anti-tumor activity will be assessed by radiological tumor assessments and will be based on RECIST v1.1 (Appendix 2) for secondary endpoints CCI [redacted]

Increasing clinical experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of targeted therapies and/or biologics. This is particularly true for immunotherapeutic agents such as anti-CTLA-4 and anti-PD-1/anti-PD-L1 antibodies which exert their antitumor activity by augmenting activation and proliferation of T cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects.[30,31] Clinical observations of patients with advanced melanoma treated with ipilimumab, for example, suggested that conventional response assessment criteria such as RECIST and World Health Organization (WHO) criteria are not sufficient to fully characterize patterns of tumor response to immunotherapy because tumors treated with immunotherapeutic agents may show additional response patterns that are not described in these conventional criteria.[32] Furthermore, the conventional tumor assessment criteria (RECIST and WHO criteria) have been reported as not capturing the existence of a subset of patients who have an OS similar to those who have experienced complete response (CR) or PR but were flagged as progressive disease (PD) by WHO criteria.[32] On these grounds, a tumor assessment system has been developed that incorporates these delayed or flare-type responses into RECIST v1.1 CCI [redacted] CCI [redacted]

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, 6 weeks after the first dose of therapy (Cycle 1 Day 1), every 6 weeks up to 1 year after the first dose of therapy, and then every 12 weeks therafter until documented disease progression regardless of initiation of subsequent anticancer therapy. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. Details are provided in Section 5.3.3.3.

Brain Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans are required at baseline and when there is a suspected brain metastasis. Bone scan (bone scintigraphy) or ^{18}fluorodeoxyglucose-positron emission tomography/CT (^{18}FDG-PET/CT) are required at baseline, then every 12 weeks only if bone metastases are present at baseline. Otherwise, bone imaging is required only if new bone mestastases are suspected. Bone imaging is also required at the time of confirmation of CR for patients who have bone metastases.

Safety Assessments: Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as reported in the Schedule of Activities.

Pharmacokinetic/Immunogenicity Assessments: PK/immunogenicity sampling will be collected as described in the Schedule of Activities and in the Schedule for Pharmacokinetic Sample Collection. To understand the PK effects of avelumab 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 of the study. Based on the emerging PK profile of avelumab, and after the dose-finding per mTPI method is complete, it may be necessary to enroll up to approximately 8 additional patients to further assess the effect of avelumab on the PK of axitinib. Since avelumab has a half-life of 3-5 days, it would not be feasible to run a lead-in to study the PK of avelumab alone. Therefore, the effect of axitinib on avelumab will be evaluated by comparing avelumab trough concentrations at steady state in the presence of axitinib with those reported for avelumab alone in prior studies.

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

Biomarker Assessments: A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and axitinib. In addition, biomarker studies of tumor and blood biospecimens will be carried out to help further understand the mechanism of action of the avelumab in combination with axitinib, as well as potential mechanisms of resistance.

1. CCI [redacted]

2. CCI [redacted]

3.1.1. Dose Finding Phase

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

The starting doses (Dose Level 1) are avelumab 10 mg/kg IV Q2W and axitinib 5 mg BID in 2-week cycles.

3.1.1.2. Dose-Finding Criteria

Dose finding will follow the mTPI method,[29] using doses of avelumab and axitinib as shown in Table 1.

Table 1. Dose Levels in the Dose Finding Phase

Dose Level	Avelumab	Axitinib
1 (Starting Dose Level)	10 mg/kg IV Q2W	5 mg oral BID
-1A	5 mg/kg IV Q2W	5 mg oral BID
-1B	10 mg/kg IV Q2W	3 mg oral BID

BID: twice daily; Q2W: every 2 weeks

Dose de-escalation to DL-1A and DL-1B

Possible dose-finding scenarios based on the starting dose level (1) tolerability are illustrated in Table 2. DL-1A and DL-1B will be explored only if the design recommends de-escalation at DL1.

In this dosing algorithm, there are up to 3 potential dose levels (DL): (DL1) avelumab 10 mg/kg Q2W + axitinib 5 mg BID, (DL-1A) avelumab 5 mg/kg Q2W + axitinib 5 mg BID, and (DL-1B) avelumab 10 mg/kg Q2W + axitinib 3 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 dose-finding sequences for avelumab in combination with 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 throughout the course of the study. Possible sequences are listed below in Table 2.

Table 2. Possible Dose Finding Sequences

Possible Sequences Starting with Dose Level 1
a) DL1
b) DL1 → DL-1A and DL-1B
c) DL1 → DL-1A and DL-1B → DL1

DL: dose level

Dosing will begin at DL1 and possibly be de-escalated to DL-1A and DL-1B according to Table 1 and Table 2.

Dose escalation from DL-1 back to DL1 will be allowed as long as DL1 has not been determined to have exceeded the MTD and the rule indicates escalation for both DL-1A and DL-1B. The escalation/de-escalation rules will follow the mTPI method.[29]

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
Number of Toxicities	0	E	E	E	E	E	E
	1	D	S	S	S	S	E
	2		DU	D	S	S	S
	3			DU	DU	D	D
	4				DU	DU	DU
	5					DU	DU
	6						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
Note: for the initial dose level (ie, "DL1") evaluated, the doses are maintained ("S"), while DL-1A or DL-1B may be escalated ("E").

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

- 0 - 1 DLTs → 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-1A and DL-1B and the total number of patients then treated at DL-1A and DL-1B is 3, the following dosing rules are applied within each dose level:

- 0 DLTs (in DL-1A and DL-1B) → escalate back to DL1;
- 1 DLT (in either DL-1A or DL-1B) → remain at the same DL (DL-1);
- 2-3 DLTs (in either DL-1A or DL-1B)→ de-escalation not possible and depending on the distribution of the DLTs one or both doses at DL-1 will be considered intolerable.

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

- The target enrollment cohort size is 3 patients. However, patients may be enrolled in cohort sizes of 3-4 depending on the number of potential patients identified at participating sites. The patients treated at each dose level may initiate dosing simultaneously. 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.

- The next cohort may be enrolled when all patients at the current dose cohort have been evaluated for 4 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 2 cycles of axitinib or 2 infusions of avelumab 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 6 DLT-evaluable patients have been treated at the highest dose associated with DLT rate <0.33. It is estimated that approximately 15 DLT-evaluable patients will need to be enrolled to reach 6 DLT-evaluable patients at the estimated MTD.
- 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, PK, and PD involving all available data from test cohorts.

3.1.2. Dose-Limiting Toxicity Definition

Severity of adverse events will be graded according to CTCAE version 4.03 (see Appendix 4). For the purpose of dose finding, any of the following adverse events occurring during the primary DLT observation period (4 weeks, from the time of first administration of avelumab [Cycle 1 Day 1] until the planned administration of the third dose of avelumab [Cycle 3 Day 1]) that are attributable to one, the other, or both agents in combination will be classified as DLTs:

- Hematologic:
  - Grade 4 anemia;
  - Grade 4 neutropenia lasting >7 days;
  - Febrile neutropenia, defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3 degrees C (>101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour;
  - Grade ≥3 neutropenic infection;
  - Grade ≥3 thrombocytopenia with bleeding;
  - Grade 4 thrombocytopenia.
- Non-Hematologic (including Non-Laboratory):
  - Any Grade ≥3 toxicity, **except** for any of the following:

- Transient (≤6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management;
- Transient (≤24 hours) Grade 3 fatigue, local reactions, or headache that resolves to Grade ≤1;
- Grade 3-4 nausea and vomiting controlled by optimal medical therapy within 72 hours;
- Grade 3 hypertension controlled by medical therapy;
- Grade 3 diarrhea or Grade 3 skin toxicity that resolves to Grade ≤1 in less than 7 days after medical management (eg, immunosuppressant treatment) has been initiated;
- Any Grade ≥3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis;
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

- Grade 3-4 liver function test elevation (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) concurrent with Grade 2 elevation of total bilirubin.
- Non-hematologic Grade ≥3 laboratory abnormality if medical intervention is required to treat the patient, or if the abnormality leads to hospitalization.
  - Single laboratory values out of normal range that are unlikely related to trial treatment according to the investigator, do not have any clinical correlate, and resolve to Grade ≤1 within 7 days with adequate medical management **<u>are not</u>** to be considered DLTs.

- Inability to complete at least 75% of the first 2 cycles doses of axitinib (starting from Cycle 1 Day 1 after completion of the Lead-in PK period) or 2 infusions ofavelumab within the DLT observation period due to investigational product-related toxicity.

In absence of associated clinical abnormalities, abnormal laboratory tests should be repeated to confirm relevance. While the rules for adjudicating DLTs in the context of dose finding/dose expansion phases are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between sponsor and investigator, based on the emerging safety profile.

3.2. Maximum Tolerated Dose Definition

The MTD estimate is the highest dose level tested of avelumab and axitinib associated with the occurrence of DLTs within the first 2 cycles of treatment in <33% of DLT-evaluable patients.

3.3. Dose Expansion Phase Test Dose Definition

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

3.3.1. Dose Expansion Phase

The Dose Expansion Phase Test Dose identified in the Dose Finding Phase will be expanded up to an additional 40 patients with the purpose of confirming the safety, efficacy, PK, and PD of that dose.

In case both DL-1A and DL-1B regimens are identified as Dose Expansion Phase Test Doses, both of them will be expanded up to an additional 40 patients randomly enrolled in each arm.

3.4. Recommended Phase 2 Dose Definition

The RP2D is the dose of avelumab and axitinib in combination chosen for further studies based on Phase 1 study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of patients, then this dose usually becomes the RP2D. Further experience with the MTD may result in a RP2D dose lower than the MTD. Attention will be given to the percentage of patients that discontinue treatment due to treatment-related AEs, especially (both early and late occurring) immune-related (dose-limiting) toxicities.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Diagnosis:

    - Histologically or cytologically confirmed advanced RCC with clear cell component;

- Primary tumor resected;

- A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from a *de novo* tumor biopsy obtained during screening will be required (biopsied tumor lesion should not be a RECIST target lesion). Alternatively, a recently obtained archival FFPE tumor tissue block (not cut slides) from a primary or metastatic tumor resection or biopsy can be provided if the following criteria are met: 1) the biopsy or resection was performed within 1 year of enrollment AND 2) the patient has not received any intervening systemic anti-cancer treatment from the time the tissue was obtained and enrollment. If an FFPE tissue block cannot be provided as per documented regulations 15 unstained slides (10 minimum) will be acceptable (see Section 6.1.1).

- Availability of an archival FFPE tumor tissue block from primary diagnosis specimen (if available and not provided per above). If an FFPE tissue block cannot be provided, as per documented regulations, 15 unstained slides (10 minimum) will be acceptable (see Section 6.1.1);

- At least one measureable lesion as defined by RECIST version 1.1 that has not been previously irradiated.

2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guidance/practice) has been informed of all pertinent aspects of the study.

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

4. Age ≥18 years. (≥20 years in Japan).

5. Estimated life expectancy of at least 3 months.

6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see Appendix 1.

7. 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 ≤140 mm Hg, and the baseline diastolic BP readings must be ≤90 mm Hg. Use of antihypertensive medications to control BP is allowed.

8. Adequate bone marrow function, including:

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

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

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

9. Adequate renal function, including:

    a. Estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault (CG) equation;

    b. Urinary protein <2+ by urine dipstick. If dipstick is ≥2+, then 24-hour urinary protein <2 g per 24 hours.

10. Adequate liver function, including:

    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN);

    b. AST and ALT ≤2.5 x ULN.

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

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

4.2. Exclusion Criteria

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

1. Any of the following prior cancer therapies:

    - Prior systemic therapy directed at advanced RCC;
    - Prior adjuvant or neoadjuvant therapy for RCC if disease progression or relapse has occurred during or within 12 months after the last dose of treatment;
    - Prior immunotherapy with IL-2, IFN-α, or 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 immune checkpoint pathways;
    - Prior therapy with axitinib as well as any prior therapies with other VEGF pathway inhibitors.

2. Participation in other therapeutic studies within 4 weeks prior to enrollment in the current study.

3. Patients with known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.

4. Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to enrollment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to enrollment.

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

6. Current or prior use of immunosuppressive medication within 7 days prior to enrollment, except the following:

   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
   - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
   - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

7. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3), any history of anaphylaxis.

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

9. Diagnosis of any other malignancy within 5 years prior to enrollment, 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).

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

11. Gastrointestinal abnormalities including:

    - Inability to take oral medication;
    - Requirement for intravenous alimentation;
    - Prior surgical procedures affecting absorption including total gastric resection;
    - Treatment for active peptic ulcer disease in the past 6 months;

- Active gastrointestinal bleeding, unrelated to cancer, as evidenced by clinically significant hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;

- Malabsorption syndromes.

12. Active infection requiring systemic therapy.

13. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

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

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

16. 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.

17. Evidence of inadequate wound healing.

18. Grade ≥3 hemorrhage within 4 weeks of patient enrollment.

19. Any of the following within the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack deep vein thrombosis, or symptomatic pulmonary embolism.

20. Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4/5 inhibitors, including their administration within 10 days prior to patient enrollment (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos], ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

21. Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers, including their administration with 10 days prior to patient enrollment(eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St John's wort).

22. 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 study.

23. Pregnant female patients, breastfeeding female patients.

24. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, uncontrolled asthma, and pneumonitis or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, 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, patients will receive avelumab (for which the teratogenic risk is currently unknown) in combination with axitinib, which has been associated with teratogenic risk.

The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected an appropriate method of contraception for the individual patient or her partner from the permitted list of contraception methods (see Section 4.3.1.4) and will confirm that the patient has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities (SoA), the investigator or designee will inform the patient of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the patient's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception).

Patients must agree to use at least 1 of the selected methods of contraception throughout the study and continue to do so for at least 30 days after the last dose of study treatment.
In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

4.3.1.1. Male Participant Contraception

Male patients with female partner of childbearing potential must agree to use a male condom during the intervention period and for at least 30 days after the last dose of study treatment.

4.3.1.2. Female Participant Reproductive Status

A female patient is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a Women of Childbearing Potential (WOCBP) (see definitions in Section 4.3.1.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 30 days after the last dose of study treatment. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

4.3.1.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

        - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

        - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.3.1.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - oral;

    - intravaginal;

    - transdermal;

    - injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - oral;
    - injectable.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

If exposure during pregnancy will occur, please refer to Section 8.10 Exposure During Pregnancy.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigator site file.

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 numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patients participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For the purpose of this study the investigational products are avelumab (MSB0010718C) and axitinib (AG-013736).

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. In case DL-1A and DL-1B both are investigated, 6 patients will be randomly assigned to either dose levels (1:1 treatment allocation, 3 patients per dose level).

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 (8 digits, of which 4 belong to the site identifier number), which will be used on all Case Report Form (CRF) pages and other trial-related documentation or correspondence referencing that patient. Demographic information will also be required.

The sponsor will fax or e-mail the approved Registration Form reporting the patient identification number to the site. See also Schedule of Activities table.

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

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

The sponsor or designee will notify the other sites of the inclusion of a new patient, and will inform study sites about the next possible enrollment date. Study treatment (either single-agent axitinib for patients in Lead in or avelumab in combination with axitinib for all other patients) should begin within 3 days after enrollment or randomization. See Schedule of Activities table.

5.2. Patient Compliance

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 at each clinic visit. 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 (±3 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. Investigational Product Supplies

Avelumab (MSB0010718C) and axitinib (AG-013736) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Axitinib

Axitinib will be supplied as 1 mg and 5 mg film-coated tablets for oral administration in light-resistant high-density polyethylene (HDPE) bottles with desiccant.

5.3.1.2. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20.0 mg/mL solution and will be supplied by the sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines. Avelumab will be packed in boxes each containing one vial. The information on the study treatment will be in accordance with approved submission documents.

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

5.3.2. Preparation and Dispensing

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

5.3.2.1. Avelumab

Avelumab will be dosed at the investigational site.

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

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

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

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

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

5.3.2.2. Axitinib

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 treatment via a unique container number using the Interactive Response Technology (IRT) system.

Axitinib will be dispensed every 6 weeks or as otherwise indicated. Patients should be instructed to keep their study treatment 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 study treatment to the clinic.

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

5.3.3. Administration

All investigational products will be administered on an outpatient basis.

5.3.3.1. Avelumab

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

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

Avelumab will be administered as a 1-hour IV infusion once every 2-weeks. In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate. Sites should make every effort to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes and +20 minutes is permitted (ie, infusion time is 60 minutes: -10 min/+20 min). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.3.5.5.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle. If the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of study drug required for preparation and administration for the current cycle must be recalculated using this most recent weight obtained. For weight changes ≤10% compared to the weight used to calculate the prior dose, the decision on whether to recalculate the avelumab dose will be made in accordance with local practices. Avelumab dose reduction for toxicity management is not permitted, however next cycle administration may be omitted due to persisting toxicity as described in Table 5 and Section 5.3.5.

5.3.3.2. Axitinib

Axitinib will be administered orally BID at approximately the same time in the morning and evening on a continuous dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity (see Section 5.3.5). 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 axitinib.

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 before the next scheduled dose of that day, 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 or extra doses) in a dosing diary supplied by the site. If doses are missed or vomited or if an extra dose is taken, this must be indicated in the source documents and CRFs.

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

5.3.3.3. Treatment after Initial Evidence of Radiologic Disease Progression

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

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

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

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

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

If the repeat imaging confirms PD, patients should be discontinued from study treatment. However, according to the investigator's clinical judgment and after discussion between the investigator and the sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with single agent avelumab, axitinib, or avelumab combined with axitinib. 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 who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression thereafter will be eligible for re-treatment with avelumab at the discretion of the investigator and after discussion with the sponsor's medical monitor if 1) no cancer treatment was administered other than axitinib since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, and 3) the trial is still open. Patients will resume avelumab therapy at the same dose and schedule applied at the time of discontinuation.

5.3.4. Food Requirements

Both investigational products may be administered without regard for food, but patients must avoid foods that are known strong CYP3A4/5 inhibitors (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]).

5.3.5. Recommended Dose Modifications

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

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom. In addition to dose modifications, 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.

For axitinib dose modifications may occur in 2 ways:

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

For avelumab, no dose modifications are permitted in this study, but next infusion may be omitted based on persisting toxicity, as outlined in Table 5.

Dose modifications and infusion omissions may occur independently for the two drugs used in this study and will be reported in the CRF.

Available axitinib dose levels for intrapatient dose modification are listed in Table 4.

5.3.5.1. Intrapatient Axitinib Dose Escalation and Dose Reduction

In the Dose Finding Phase, intrapatient axitinib dose escalation is not permitted for patients treated at DL-1A.

Intrapatient axitinib dose escalation is permitted for patients treated in the Dose Finding Phase at DL-1B (avelumab 10 mg/kg Q2W + axitinib 3 mg BID). In these patients, after the completion of the primary DLT observation period (4 weeks), intrapatient axitinib dose escalation to 5 mg BID may occur according to the criteria reported below.

In the Dose Expansion Phase, intrapatient axitinib dose escalation up to 10 mg BID may occur according to the criteria reported below.

Criteria for Intrapatient Dose Escalation: Patients who tolerate the current axitinib dose without Grade >2 drug-related adverse events for 2 consecutive weeks (in the Dose Expansion Phase) or 4 consecutive weeks (in the Dose Finding Phase, only DL-1B), and who do not experience BP >150/90 mm Hg or concurrent administration of antihypertensive medication, have the option to have their axitinib dose increased (by one dose level at a time [Table 4]). Patients treated in the Dose Finding Phase at DL-1B have the option to have their axitinib dose increased to a maximum dose of 5 mg BID. Particular attention should be provided to a patient's overall safety profile prior to implementing intrapatient axitinib dose escalation.

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

Patients will be monitored closely for toxicity, and axitinib treatment may be adjusted by dosing interruption with or without dose reduction as indicated in Table 4. Dosing interruption and/or dose reduction by 1, and if needed, up to 2 dose levels (one dose level reduction at a time) will be allowed depending on the type and severity of toxicity encountered. Management of patients requiring more than 2 dose reductions should be discussed with the sponsor's medical monitor.

Patients who have undergone dose reduction may also undergo dose re-escalation back to the previous dose level at the discretion of the Investigator in the absence of Grade ≥2 non- hematologic treatment-related toxicity for at least 28 days.

5.3.5.2. 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 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 disturbances), although a different blood pressure threshold for contacting the site may be used according to the investigator's clinical judgment.

Blood pressure should be well-controlled prior to initiating axitinib, and patients should be monitored for hypertension. To treat an increase in BP, standard antihypertensives may be used (for example, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and dihydropyridine [DHP] calcium channel blockers.[33,34]

5.3.5.3. Axitinib Dose Modifications and Avelumab Infusion Omissions for Treatment-Related Toxicity

Recommended axitinib dose modifications and avelumab infusion omissions in case of drug-related toxicity are shown in Table 5. These guidelines might be further modified at the discretion of the sponsor based on the emerging safety profile of the combination. The investigator should discuss with the sponsor's medical monitor any dose modification and or treatment discontinuation in case of persistent toxicity that would lead to dose modification or treatment discontinuation per toxicity management guidelines. Consult with the sponsor's medical monitor before discontinuing the patient.

Consider consulting with the sponsor's medical monitor for Grades 1 and 2 drug-related toxicities (Table 5), and always consult with the sponsor's medical monitor for Grades 3 and 4 drug-related toxicities (Table 5).

Table 5. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
Hematologic Abnormalities	Grade 1	• Continue at the same dose level.	• Continue as per schedule.
	Grade 2	• Continue at the same dose level.	• Continue as per schedule.
	Grade 3	• Continue at the same dose level.	• Withhold avelumab • Re-initiate avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicities does not resolve to Grade ≤1 or baseline within 12 weeks (consult with the sponsor's medical monitor before permanently discontinuing the treatment). • **Exceptions are**: Laboratory values that do not have any clinical correlate.
	Grade 4	• Withhold until recovery to Grade ≤2. • Then, reduce by 1 dose level and resume treatment. • For Grade 4 lymphopenia not associated with clinical events (eg, opportunistic infection) axitinib treatment may continue without interruption.	• Permanently discontinue avelumab (consult with the sponsor's medical monitor before permanently discontinuing the treatment). • **Exceptions are:** Laboratory values that do not have any clinical correlate.
Proteinuria	Dipstick negative or shows 1+ (Grade 1)	• Continue at the same dose level.	• Continue as per schedule.
	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	Avelumab Treatment 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 5.3.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule
	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 5.3.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
	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 5.3.5.2 for monitoring/management of axitinib-related hypertension	• Continue as per schedule.
	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 5.3.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
Infusion-related Reaction	Grade 1-4	• Continue at the same dose level.	• See Section 5.3.5.5 and Table 6
Hypersensitivity reactions	Grade 3-4	• Continue at the same dose level.	• See Section 5.3.5.6 and Table 6
Tumor lysis syndrome	Grade 1-4	• See Other Non-Hematologic Toxicities and/or Laboratory Abnormalities.	• See Section 5.3.5.7 and Figure 1

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
Immune-related AE (irAE)	Grade 1-4	• Grade 1: continue at the same dose level • Grade 2-4: hold treatment until recovery to Grade ≤1 and restart axitinib at the same dose level for Grade 2 and at reduced dose level for Grade 3-4.	• See Section 5.3.5.8 and Table 7
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 1	• Continue at the same dose level.	• Continue as per schedule.
	Grade 2	• Continue at the same dose level.	• Continue as per schedule.
	Grade 3	• Reduce by 1 dose level. • Grade 3 toxicities controlled with symptomatic medications, or Grade 3 asymptomatic biochemistry laboratory abnormalities: continue at the same dose or reduce by 1 dose level as per investigator judgment.	• Withhold avelumab. • Re-initiate avelumab once toxicity is Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline value within 12 weeks (consult with medical monitor before permanently discontinuing the treatment). **Exceptions are**: • Laboratory values that do not have any clinical correlate (eg, amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis). • Nausea and vomiting controlled by medical therapy. • Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
	Grade 4	• Hold treatment until recovery to Grade ≤2. • Then, reduce by 1 dose level and resume treatment. • Grade 4 asymptomatic biochemistry laboratory abnormality: study treatment may continue without interruption.	• Permanently discontinue avelumab (consult with the sponsor's medical monitor before permanently discontinuing the treatment). **Exceptions are:** • Laboratory values that do not have any clinical correlate.

5.3.5.4. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate.

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. If an allergic reaction occurs, the patient must be treated according to the best available medical practice. Guidelines for the emergency treatment of anaphylactic reactions are available at www.resus.org.uk/pages/reaction.pdf (Working Group of the Resuscitation Council [United Kingdom], www.erc.edu (European Resuscitation Council [European Union]), www.heart.org (American Heart Association [United States]), and www.american cpr.com (American Cardio-Pulmonary Resuscitation [CPR] Training™ [United States]). Patients should be instructed to report any delayed reactions to the investigator immediately.

Treatment recommendations for the management of infusion-related reactions, severe hypersensitivity reactions, tumor lysis syndrome, and immune-related adverse events (irAEs) are outlined in Section 5.3.5.5, 5.3.5.6, 5.3.5.7, 5.3.5.8, respectively.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at any time after the first dose of avelumab treatment. Such events may more often consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions. However, potential irAEs can occur in any organ or tissue. Treatment recommendations for the management of irAEs are outlined in Section 5.3.5.8.

5.3.5.5. Management of Avelumab Infusion-Related Reactions

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 6.

Table 6. Treatment Modification for Symptoms of Avelumab Infusion -Related Reactions

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. The total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours**.**	Stop avelumab infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect bag infusion tubing from the patient. Avelumab treatment must be permanently discontinued.

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

Once the avelumab infusion rate has been decreased by 50% due to an infusion-related reaction, it must remain so for all subsequent infusions. The total infusion time for avelumab should not exceed 120 minutes.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions

In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that cycle. At the next cycle, the investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.3.5.6. Management of Avelumab-Related Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

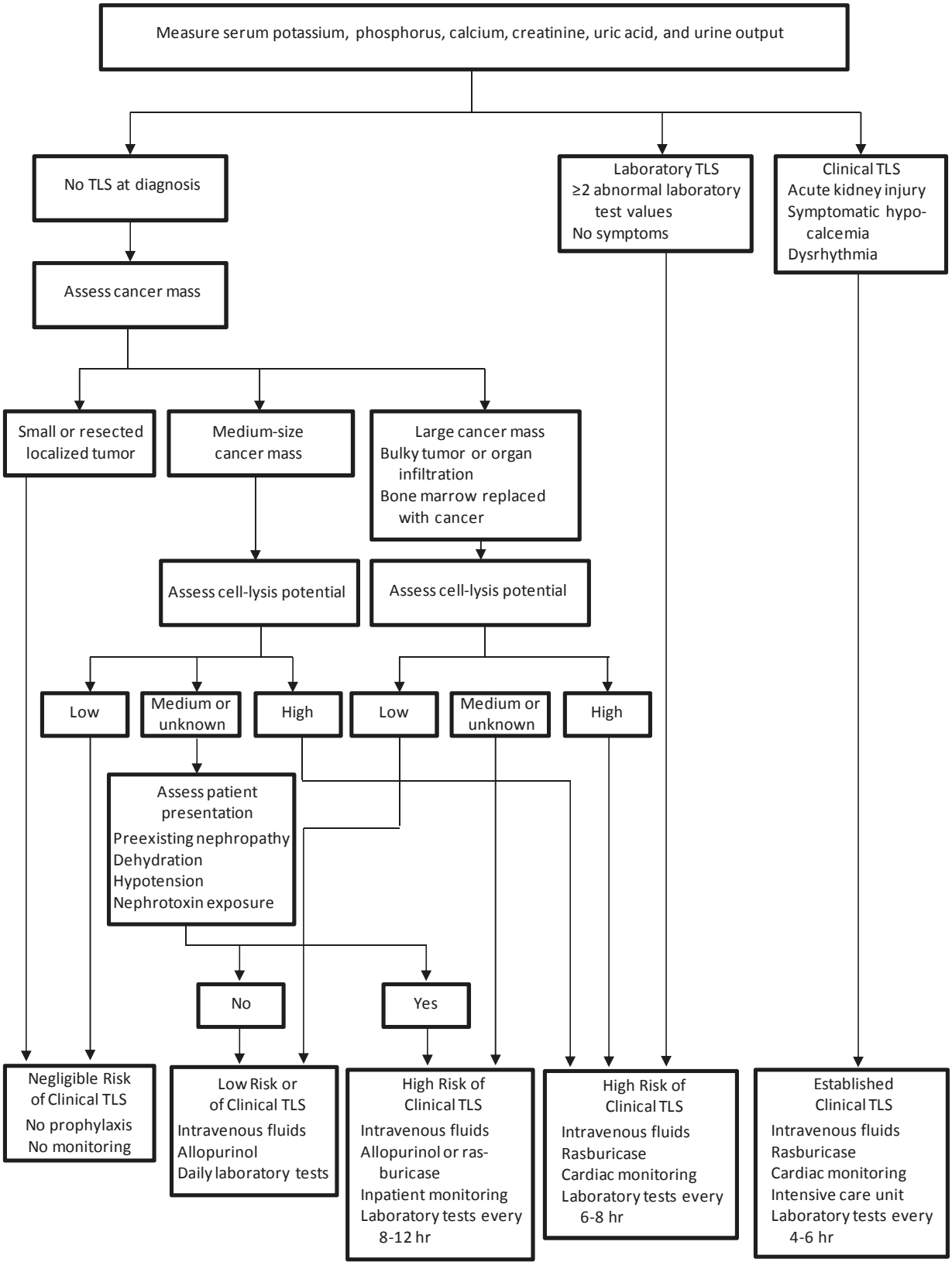
For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable non-steroidal anti-inflammatory drug (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (eg, paracetamol or ibuprofen) and rigors (eg, meperidine) may be given to patients at the discretion of the investigator.

Additional treatment recommendations for symptoms of avelumab infusion-related reactions are provided in Appendix 6 and may be modified based on local treatment standards and guidelines, as appropriate.

5.3.5.7. Management of Avelumab-Related Tumor Lysis Syndrome

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumor lysis syndrome (TLS). Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 1) published by Howard et al.[35]

Figure 1. Assessment and Initial Management of Tumor Lysis Syndrome



5.3.5.8. Management of Avelumab Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v. 4.03):

- Grade 1 to 2: treat symptomatically or with moderate-dose steroids, more frequent monitoring;
- Grade 1 to 2 (persistent): manage similar to Grade 3 to 4 AE;
- Grade 3 to 4: treat with high-dose corticosteroids.

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

Some potential irAEs described with anti-PD-L1 drugs such as avelumab may overlap with axitinib toxicities (eg, diarrhea, elevated liver function tests). Any adverse event suspected to be immune-related should be managed according to the guidance for management of irAEs in this section.

For potential overlapping Grade 2 irAEs, hold both drugs used in the combination (avelumab and axitinib) and follow the specific management recommendations described in Table 7. When the event resolves to Grade ≤1, restart therapy with axitinib. If the Grade ≥2 event does not recur, restart avelumab at the beginning of the next treatment cycle. If the Grade ≥2 event does not resolve to Grade ≤1 after holding avelumab for 2 treatment cycles (up to 28 days) or if the Grade ≥2 event recurs after re-introduction of avelumab, permanently discontinue avelumab therapy.

For potential overlapping Grade ≥3 irAEs, hold axitinib and follow the specific guidance in Table 7 for avelumab. When the event resolves to Grade ≤1, restart therapy with axitinib at reduced dose level. Avelumab should be permanently discontinued.

Table 7. Management of Avelumab Immune Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg. loperamide).	Close monitoring for worsening symptoms. Educate patient to report worsening immediately. If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in	Withhold avelumab therapy Symptomatic treatment.	If improves to Grade ≤1: Resume avelumab therapy If persists >5-7 days or recurs: Treat as Grade 3 or 4.

stool		
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy. Symptomatic therapy (for example, antihistamines, topical steroids).	If persists >1 to 2 weeks or recurs: Withhold avelumab therapy. Consider skin biopsy. Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy. Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Intial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy. Monitor for symptoms every 2 to 3 days.	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.

	Consider Pulmonary and Infectious Disease consults.	
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults. Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung Biopsy.	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung Biopsy.	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation ((NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy.	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤1: Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and /or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent.	If returns to Grade ≤1: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3

	Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ Hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy.	Continue renal function monitoring. If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy. Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.

Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 Endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement. therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH):	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary

	- Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). - Hormone replacement/suppressive therapy as appropriate. - Perform pituitary MRI and visual field examination as indicated. **If hypophysitis confirmed:** - Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month - Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. - Add prophylactic antibiotics for opportunistic infections.	gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation.	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy. If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of **Grade 3** irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate.	If improves to Grade ≤1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same **Grade 3** irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month.

Grade 4	Permanently discontinue avelumab Therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. Add prophylactic antibiotics for opportunistic infections. Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy. Specialty consult.	

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

5.4. Investigational Product Storage

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 product should be stored in its original container and in accordance with the label.

- Axitinib must be stored at controlled room temperature (between 15-30°C) or as specified on the label.
- Avelumab must be stored in the refrigerator (between 2-8°C) or as specified on the label.

Storage conditions stated in the SRSD (ie, investigator's brochure) will be superseded by the storage conditons stated on the 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 daily evaluation for excursions should be documented. The operation of the temperature monitoring device

and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

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

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

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) 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.

5.5. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product-supplies. All bottles of study drug must be returned to the investigator by the patient at every visit and at the end of the trial, Pfizer will provide instructions as to disposition of any unused investigational product.

5.6. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatments(s)

Medications or vaccinations specifically prohibited in the Exclusion Criteria (Section 4.2) are also not allowed during the active treatment period, except for administration of the inactivated influenza vaccine.

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

decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

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

All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

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

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

Recommended medications to treat infusion-related reactions, hypersensitivity reactions, flu-like symptoms, tumor lysis syndrome and immune-related events are reported in Sections 5.3.5.5, 5.3.5.6, 5.3.5.7, and 5.3.5.8, respectively.

5.7.1. Inhibitors and Inducers of CYP Enzymes

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 adjustments have not been studied in patients receiving strong CYP3A4/5 inhibitors, consider dose reduction if axitinib must be used with a CYP3A4/5 inhibitor.

If coadministration of the strong CYP3A4/5 inhibitor is discontinued, the axitinib dose should be re-escalated (after 10 days) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Coadministration 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. Consider dose escalation if axitinib must be used with a CYP3A4/5 inducer.

If coadministration of the strong CYP3A4/5 inducer is discontinued, the axitinib dose should be de-escalated (after 10 days) to that used prior to initiation of the strong CYP3A4/5 inducer.

5.7.2. Hematopoietic Growth Factors

Granulocyte colony-stimulating factor may be used in agreement with American Society of Clinical Oncology (ASCO) guidelines.[46]

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 if clinically indicated.

5.7.3. Concomitant Surgery

No formal studies of the effect of axitinib on wound healing have been conducted; however, caution is advised based on the mechanism of action. If a major surgery or an interventional procedure (eg, endoscopy) is required, treatment with axitinib must be interrupted at least 24 hours before the procedure, and the patient BP should be monitored closely for hypotension. Patients may resume axitinib 7 days after minor surgery and 2-3 weeks after major surgery, assuming the wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

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

5.7.4. Concomitant Radiotherapy

Local radiotherapy (limited field) of isolated lesions with palliative intent is acceptable and allowed throughout the study (ie, starting from the screening through end of treatment) 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 pain, the site(s) of disease causing pain should be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression. The Medical Monitor should be consulted prior to starting radiotherapy and prior to restarting study treatment after the end of radiotherapy.

5.7.5. Other Prohibited Concomitant Medications and Therapies

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

- Immunotherapy, immunosuppressive drugs (ie, chemotherapy or systemic corticosteroids except for short-term treatment of allergic reactions or for the treatment of irAEs). Short-term administration of systemic steroids (eg, for allergic reactions or the management of irAEs) is allowed. Topical and inhalation steroids are allowed.

- Any vaccine therapies for the prevention of infectious disease within 4 weeks after the start of study treatment, except administration of the inactive influenza vaccine.

- Bisphosphonate or denosumab treatment is not allowed unless it has been initiated more than 14 days prior to receiving the first administration of avelumab.

- Anti-cancer systemic chemotherapy or biological therapy or investigational agents other than avelumab and axitinib.

- Other experimental pharmaceutical products.

- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes.[36,37] Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA-4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes.[38] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 7.

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

- Prophylactic use, eg, for the prevention of acute infusion-related reactions: is prohibited, ***except*** prior to CT or MRI scan.

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

5.8. Rescue Medications and Supportive Care

5.8.1. 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. Prophylactic administration should be considered for the cases outlined in Table 7.

- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

6. STUDY PROCEDURES

6.1. Screening

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

6.1.1. Tumor Biospecimens

Provision of tumor biospecimen will be required for enrollment onto the study as follows:

1. Recent tumor biospecimen: a mandatory FFPE tumor tissue block from a *de novo* tumor biopsy must be obtained from all patients during screening. The biopsied tumor lesion should not be a RECIST target lesion. CCI [redacted]
2. Archival tumor biospecimen: a mandatory archival FFPE tumor tissue block from the primary diagnosis specimen must be provided from all patients prior to enrollment/randomization. CCI [redacted]

[redacted]

3. End of Treatment Tumor Biospecimen: A *de novo* tumor sample (ie, fresh biopsy) should also be collected at the time of discontinuation of either drugs and at the End of Treatment unless clinically contraindicated.

For all tumor biospecimen, tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. The *de novo* biopsy(ies) should be FFPE as per routine (see Study Manual), and the resulting FFPE tissue block(s) or slides should be submitted to the Central Laboratory. Additional information on tumor biospecimen collection procedures is included in the Study Manual.

6.2. Study Period

For treatment period procedures, see Schedule of Activities table and Assessments section (Section 7). After amendment #4 approval, patients receiving axitinib single agent will visit the site every 6 weeks. Between site visits, AEs and concomitant medications collection will be performed every 2 weeks by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.

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

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

6.4. End of Study

The study will end after all treated patients have died, been lost to follow-up or have withdrawn consent to be followed for survival.

6.5. Patient Withdrawal

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

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single-agent avelumab or axitinib, or with avelumab in combination with axitinib , provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.3.3.3);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the sponsor) may continue treatment with the other study treatment;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

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

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

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, then no further evaluations should be performed, and no additional data should be collected. The sponsor will 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 or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as described in the Schedule of Activities table.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on up to 3 occasions prior to starting combination study treatment - once at the start of screening (all patients), and once at Lead-in Day 1 (patients in Dose Finding Phase only and up to approximately 8 additional patients enrolled for further PK assessment) immediately before axitinib administration, and at the Cycle 1 Day 1 visit (all patients) immediately before the administration of avelumab in combination with axitinib. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Additional pregnancy tests (serum or urine) will also be routinely repeated at every cycle during the active treatment period, at the end of study treatment, and during short tem Fu period, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from treatment but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Board/Ethics Committees (IRB/ECs) or if required by local regulations.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by NCI CTCAE version 4.03), timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessments

Haematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities table and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 8. Clinically significant abnormal laboratory results shoud be repeated as soon as possible (preferably within 24-48 hours) and followed up as per standard clinical practice unless otherwise specified in this protocol.

If a full and core chemistry panel are scheduled at the same visit, then only the full chemistry panel will be performed.

Table 8. Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	After amendment #4 approval Chemistry Panel (# denotes test to be performed only when clinically indicated)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	ALT	Protein, glucose, blood. Urine dipstick/other semiquantitative method, for urine protein: if ≥2+, collect 24-hour	PT, INR	For female patients of childbearing potential, serum or urine
Platelets	AST*	AST		PTT or aPTT	
WBC	Alkaline Phosphatase*	Alkaline Phosphatase			
Absolute Neutrophils	Sodium*	Sodium			
Absolute Lymphocytes	Potassium*	Potassium			
Absolute Monocytes	Magnesium*	Magnesium			
Absolute Eosinophils	Chloride*	Chloride			
Absolute Basophils	Total Calcium*	Total Calcium			
	Total Bilirubin* °	Total Bilirubin °			
	BUN or Urea*	BUN or Urea			
	Creatinine*	Creatinine			
	Glucose (non-fasted)*	Glucose (non-fasted)			
	Phosphorus or Phosphate*	Phosphorus or Phosphate			
	Albumin	Albumin[#]			
	Total Protein	Total Protein[#]			
	Uric Acid	Uric Acid[#]			
	Amylase	Amylase			
	Gamma glutamyl transferase (GGT)	Gamma glutamyl transferase (GGT)			
	Cholesterol	Cholesterol[#]			
	Creatine kinase	Creatine kinase			
	C-reactive protein (CRP)	C-reactive protein (CRP) [#]			
	Lactate dehydrogenase (LDH)	-			
	Lipase	Lipase			
	Triglycerides	Triglycerides[#]			
	Other tests: HBV, HCV				
	Thyroid Function Tests: TSH, free T4				

	Other Tests: ACTH			

° 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.

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV= hepatitis B Virus, HCV= hepatitis C Virus, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cell.

7.1.4. Vital Signs and Physical Examination

Physical examinations will be performed according to institutional guidelines on study days as described in the Schedule of Activities table.

The physical examination will include major body systems, weight (height will be measured at screening only), assessment of ECOG performance status.

Vital signs (blood pressure, pulse rate) will be measured at the time points described in the Schedule of Activities table. 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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit (every 6 weeks after amendment #4 approval).

In addition, all patients will be monitoring BP at home as described in Section 5.3.5.2.

7.1.5. (12-Lead) Electrocardiogram Measurements

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECG assessments.

All patients require a triplicate ECG measurement at screening and on treatment. On-treatment ECGs will be performed on Lead-in Day 7 (patients in Dose-Finding Phase and and up to approximately 8 additional patients enrolled to assess the effect of avelumab on the PK of axitinib), Cycle 1 Day 1 (all patients), Cycle 4 Day 1 (all patients), and End of Treatment/Withdrawal. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). Triplicate ECGs at Cycle 1 Day 1 will be prior to avelumab infusion and within 30 minutes post end of -infusion. When coinciding with blood sample draws for PK, ECG assessment should be performed prior to blood sample collection such that the blood sample is collected at the nominal time.

Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc >500 msec (ie, CTCAE Grade >2), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If the manual reading verifies a rate corrected QTc of >500 msec, a repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to conclusion that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist. If QTc interval reverts to less than 500 msec, and in the judgment of investigator and sponsor is determined to be due to a cause other than study drug, treatment may be continued with regular ECG monitoring.

If patient experiences a cardiac or neurologic AE (eg, syncope, dizziness, seizures, or stroke), then triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.

7.2. Pharmacokinetics Assessments

Plasma/serum samples will be obtained from patients for PK analysis of avelumab and axitinib depending on the study phase (Dose Finding or Dose Expansion) that they belong to. Samples for avelumab PK will be collected from all patients in the study. Axitinib PK samples will be collected from all patients in the Dose Finding Phase and, if needed, up to approximately 8 additional patients enrolled to assess the effect of avelumab on the PK of axitinib.

7.2.1. Blood Sample Collection for Pharmacokinetic Analysis

Where noted in the Schedule of Activities table, 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 avelumab in combination with axitinib. For all PK blood sample collections, the actual time of avelumab and axitinib dosing, as well as actual times of PK collections, will be recorded in the source documents and CRF. 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 PK sample collection visits. Patients who do not take the scheduled axitinib doses for 3 consecutive days prior, must reschedule PK sample collections to a future date. If this occurs in the axitinib Lead-in period, it may delay Cycle 1 Day 1; if it occurs during treatment cycles, it may delay Cycle 4 Day 1 avelumab infusion. For all PK collections, the actual time of avelumab and axitinib dosing, as well as actual times of PK collections will be recorded in the source documents and CRF.

Blood samples for axitinib PK and avelumab PK will be collected as outlined in the Schedule for Pharmacokinetic Sample Collections table. PK sampling schedule may be modified based on emerging PK data.

PK samples for avelumab will also be collected at the Day 30 Follow-up visit after the end of avelumab treatment.

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

All efforts will be made to obtain the PK 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 compliant, 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 the investigator and sponsor.

PK samples will be assayed for avelumab and axitinib 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 PK of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for avelumab and axitinib. The results of such analyses may be included in the clinical report.

7.2.2. Collection of Axitinib Pharmacokinetic 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 axitinib PK analysis.

7.2.3. Collection of Avelumab Pharmacokinetic Samples

A total of 3.5 mL of whole blood will be collected into a serum separator tube (SST) at the designated times to provide serum for avelumab PK analysis.

7.3. Immunogenicity Assessment

A total of 3.5 mL of whole blood will be collected into a SST at the designated times to provide serum for evaluation of avelumab immunogenicity. Immunogenicity blood samples will be assayed for anti-avelumab antibodies using a validated analytical method. All of the samples that are positive for ADA may also undergo characterization for neutralizing antibodies. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.4. Translational and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of avelumab and axitinib. In addition, analyses of sequentially obtained 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.

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Tumor biopsies obtained at the time of discontinuation of either drugs and at the End of Treatment will be used to investigate acquired mechanisms of resistance. Only core needle or excisional biopsies, or resection specimen are suitable. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Study Manual.

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7.6. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans; it may also include brain CT or MRI scan at baseline and whenever brain metastases are suspected. The CT and MRI 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, at 6 weeks after the first dose of therapy (Cycle 1 Day 1), then every 6 weeks up to 1 year from the first dose of therapy, and then every 12 weeks thereafter until documented disease progression regardless of initiation of subsequent anticancer therapy. 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). CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiological imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. See Schedule of Activities table and Section 5.3.3.3 for treatment after initial evidence of disease progression.

Brain CT or MRI scans are required at baseline and when there is a suspected brain metastasis. Bone scan (bone scintigraphy) or ^{18}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 complete response for patients who have bone metastases. Otherwise, bone imaging is required only if new bone metastases are suspected and at the time of confirmation of CR 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) CCI [redacted]

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

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the study treatment.

SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through and including 90 calendar days after the last administration of study treatment. If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

- Drug abuse;
- Drug dependency.

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

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

8.3.1. Avelumab Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 5.3.5.8. AESIs are reported according to the general AE reporting rules specified in Section 8.1 and 8.2.

8.4. Medication Errors

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

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

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

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

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

For axitinib, an overdose is defined as a dose greater than 10 mg BID.

There is no specific treatment for overdose of avelumab or axitinib. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE (version 4.03) Grade 5 (see the section on Severity Assessment).

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

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

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

- Concurrent with:

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

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

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

GRADE	Clinical Description of Severity
0	No Change from normal or reference range (This grade is not included in the Version 4.03 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.

8.9. Causality Assessment

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

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

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

8.10. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion.

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

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

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (see Also the Section on Patient Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/parent(s)/legal guardian/legally acceptable representative. In addition, each study patient/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study 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:

- Full Analysis Set.

  The full analysis set includes all patients who receive at least 1 dose of study drug (axitinib or avelumab) and all patients who are randomized independent of whether they received a dose of study drug. Patients will be classified according to the treatment actually received or according to the treatment assigned at randomization if randomization occurs in this study.

- Safety Analysis Set.

  The safety analysis set includes all enrolled patients who receive at least 1 dose of avelumab or axitinib.

- Per Protocol Analysis Set (Dose Finding Phase; evaluable for DLT).

  The per protocol analysis set includes all enrolled patients during the Dose Finding Phase who:

  - Receive at least 1 dose of avelumab and axitinib; and
  - Either experience DLT during the first 2 cycles of combination axitinib + avelumab treatment, or complete the primary DLT observation period for the first 2 cycles of combination treatment (4 weeks).

  Patients who withdraw from study treatment before receiving at least 75% of the planned first 2 cycles of axitinib starting from Cycle 1 Day 1 after completion of the Lead-in PK period or 2 infusions of avelumab within the primary DLT observation period due to reasons other than investigational product-related adverse events are not evaluable for DLT.

- PK Analysis Set.

  The PK analysis set is defined as all enrolled patients who receive at least 1 dose of avelumab or axitinib and who have at least 1 concentration above the below limit of quantitation (BLQ) of either study drug.

  The PK parameter analysis set is defined as all enrolled patients who receive at least 1 dose of avelumab or axitinib and who have at least 1 of the PK parameters of interest of either study drug.

- Immunogenicity Analysis Set.

  The immunogenicity analysis set is defined as all enrolled patients who receive at least 1 dose of avelumab or axitinib and who have at least 1 ADA sample collected.

- Biomarker Analysis Set.

  The biomarker analysis set is defined as all enrolled patients who have at least one screening biomarker assessment and who receive at least 1 dose of avelumab or axitinib. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.2. Statistical Methods and Properties

9.2.1. Statistical Methods for Dose 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[29] is an interval-type of design that uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference in probability between the toxicity rate of each dose level to the target rate (pT = 0.33). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model.

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

Decision rules are based on calculating unit probability mass (UPM) of 3 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 Avelumab as a single-agent in Study EMR100070-001, 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 3 dosing intervals are associated with 3 different dose-escalation decisions. The under-dosing interval corresponds to a dose escalation (E), over-dosing corresponds to a dose de-escalation (D), and proper-dosing corresponds to remaining at the current dose (R). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length

of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the under-dosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Ji and collaborators[29] 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 (Phase 1) uses a modified version of the mTPI design that maximizes the number of evaluable patients treated at each dose level at 6. Dose finding is completed when 6 evaluable patients have been treated at the highest dose with DLT rate <0.33.

9.3. Sample Size Determination

The sample size planned for the dose finding part arises from logistic feasibility and is not entirely driven by statistical considerations. Due to the dynamic nature of the dose allocation procedure and unknown safety profile of the combination, the sample size of the interval design cannot be determined in advance. It is expected that approximately 15 DLT-evaluable patients will be required for the dose finding phase.

Up to approximately 40 patients will be included in the dose expansion phase of the study for each MTD dose level cohort expanded. A sample size of 40 patients will provide at least 90% probability to observe at least 1 AE if the true incidence of the AE in the population is ≥6%.

Based on the emerging PK data and after the completion of the dose-finding part of study phase on mTPI method, it may be necessary to enroll up to approximately 8 additional patients to further assess the effect of avelumab on the PK of axitinib. These additional patients will undergo the same evaluations and procedures as those described in the Schedule of Activities for the Dose Finding Phase of the study and will be treated concurrently with the initiation of the Dose Expansion Phase.

9.4. Efficacy Analysis

In this study, assessement of 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. For patients enrolled in the Dose Finding Phase, only data listings for best overall response (BOR) may be presented.

This study may include randomization to study treatments (see Section 5.1). Efficacy endpoints will be defined based on **'start date'** which is the start date of study treatment for patients who are not randomized, or the date of randomization for patients who are randomized to DL-1A or DL-1B.

9.4.1. Analysis of Efficacy Endpoints

Efficacy data will be analyzed by treatment group based on the full analysis set for patients enrolled in the Dose Expansion Phase.

Confirmed objective Response (OR) is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the start date until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. Patients who do not have an on-treatment radiographic tumor assessment due to early disease progression, who receive anti-tumor treatments other than the study treatments prior to achieving CR or PR, or who die, experience disease progression, or drop out for any reason prior to achieving CR or PR will be counted as non-responders in the assessment of OR. OR rate (ORR) is defined as the proportion of patients who have an OR.

Disease Control (DC) is defined as OR (CR or PR) or stable disease (SD) per RECIST v1.1 from the start date until the first documentation of objective disease progression or death due to any cause. DCR is defined as the proportion of patients with DC.

Time to Tumor Response (TTR) is defined as the time from start date 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. The censoring rules for DR are as defined below for PFS.

Progression Free Survival (PFS) is defined as the time from the start date to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to a PFS event, or for patients with a PFS event after ≥2 missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the start date unless death occurred on or before the time of the first planned post-baseline tumor assessment in which case the death will be considered an event.

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

ORR and DCR will be estimated and the corresponding exact 2-sided 95% confidence intervals will be reported. TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods. In addition, progression date, death date, date of first response, and last tumor assessment date will be listed, together with BOR, TTR, DR, and PFS.

CCI [redacted]

[redacted]

[redacted]

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics

9.5.1.1. Pharmacokinetic Analysis of Avelumab and Axitinib

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_{tau}, $t_{1/2}$, oral plasma clearance (CL/F), and apparent volume of distribution (V_z/F). Dose normalized parameters (eg, CDN-C_{max}, DN-AUC) will be reported as appropriate). Descriptive statistics for the PK parameters for axitinib will be provided by dose, cycle and day of assessment in tabular form.

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

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

9.5.1.2. Effect of Avelumab on Axitinib Pharmacokinetics

The effect of repeated avelumab dosing on axitinib PK will be evaluated based on overall assessment of the geometric mean ratios for C_{max} and AUC_{tau} of axitinib on Cycle 4 Day 1 (avelumab in combination with axitinib) in relation to Lead-in Day 7 (axitinib alone). The associated 90% confidence intervals will also be computed for the geometric mean ratios.

9.5.1.3. Immunogenecity Assessment

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

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

9.5.1.4. Population Pharmacokinetic Analysis

Avelumab disposition will be evaluated using a population PK model for the drug and will be reported separately.

9.5.1.5. Analysis of Biomarker Endpoints

Biomarkers will be assessed separately for blood and tumor tissue biospecimens. Summaries of baseline levels and, when on-treatment biomarker data is available, 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.

CCI [redacted]

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 treatment group for all treated patients using appropriate tabulations and descriptive statistics separately for each phase of the study. Safety data collected during the lead-in PK period will be reported separately. All safety data collected through 90 days after the last administration of study drug will be listed.

9.6.1. Analysis of the Primary Safety Endpoint

Dose-Limiting Toxicity (DLT) is the primary endpoint of the Dose Finding Phase of the study. The incidence of DLTs observed in the Dose Finding Phase is used to estimate the MTD (if reached) as described in Section 3.1.1.2. 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 will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible (http://ctep.info.nih.gov/reporting/ctc.html). The frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term will be reported. Adverse events will be graded by worst NCI CTCAE v4.03 severity grade, and will be summarized by cycle and by relatedness to study treatment.

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade ≥3, trial drug-related events, and serious adverse events will be considered with special attention.

Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study treatment, action taken, and clinical outcome.

9.6.2.2. Laboratory Test Abnormalities

Laboratory test results will be graded according to the NCI CTCAE v4.03 severity grade. The frequency of patients with laboratory test abnormalities will be summarized according to the worst grade for each laboratory test.

For laboratory tests without an NCI CTCAE grade definition, results will be categorized as normal (within normal ranges), abnormal, or not done.

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

9.6.2.3. Electrocardiograms

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

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

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

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

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 Safety Monitoring Committee

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

Periodic safety review procedures will include:

- Surveillance for SAEs according to regulatory guidelines.
- Discussions between the investigators and the sponsor of AEs, laboratory test abnormalities, vital signs, and ECG findings observed at each dose level in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile, make risk/benefit assessments, and decide if further enrollment is appropriate. During the Dose Finding Phase in particular, monitoring and safety findings satisfying DLT criteria will be discussed in an ongoing manner.
- Safety findings that have immediate implications for the management of patients on study will be communicated to all investigators in the timeframe associated with unexpected and drug-related SAEs.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/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).

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

12.3. Patient Information and Consent

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

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

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

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

The investigator must ensure that each study patient, or his or her legally acceptable representative (as allowed by local guideline/practice), is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

12.4. Patient Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. ECOG Performance Status

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

Appendix 2. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[45]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-Measurable Disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - One or more target measurable lesions have not been assessed;

    or

  - Assessment methods used were inconsistent with those used at baseline;

    or

  - One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

    or

  - One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective/Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 9. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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 sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

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- CCI [redacted]

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[redacted]

CCI [redacted]

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

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

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

Appendix 5. Abbreviations and Definitions of Term

^{18}FDG-PET	^{18}fluorodeoxyglucose-positron emission tomography
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
AHFS	American Hospital Formulary Service
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
ATP	Adenosine triphosphate
aRCC	Advanced renal cell carcinoma
ASHP	American Society of Hospital Pharmacists
AST	Aspartate aminotransferase
AUC	Area under the curve
BHD	Birt-Hogg-Dube
BID	Twice daily
BLQ	Below limit of quantification
BOR	Best oveall response
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CG	Cockcroft Gault
CL	Clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CR	Complete response
CRF	Case report form
CSA	Clinical Study Agreement
CT	Computerized Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events (US NCI)
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CYP1A2	Cytochrome P450 enzyme-1A2
CYP3A4/5	Cytochrome P450 enzyme-3A4/5
DAI	Dosage and Administration Instruction
DC	Disease control
DHP	Dihydropyridine
DL	Dose level
DL1	Dose Level 1
DL-1A	Dose Level -1A

DL-1B	Dose Level -1B
DLT	Dose-limiting toxicity
CCI	[redacted]
DR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EDP	Exposure during pregnancy
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FDG	Fluorodeoxyglucose
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FH	Fumarate hydratase
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRT	Hormone replacement therapy
ICH	International Committee on Harmonisation
ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International normalized ratio
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
IRB	Institutional Review Board
IRT	Interactive Response Technology

IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IV	Intravenous
kg	Kilogram
LFT	Liver function test
mAb	Monoclonal antibody
MCC	Merkel Cell Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median progression-free survival
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
mTPI	Modified toxicity probability interval
mTOR	Mammalian target of rapamycin
Nab	Neutralizing antibodies
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic
PD	Progressive disease
PD-1	Programmed death-1
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os (by mouth)
PR	Partial response
PS	Performance Status
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QD	Every day
RCC	Renal cell cancer
RSI	Reference Safety Information
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
CCI	[redacted]
SAE	Serious adverse event
SD	Stable disease
SD	Standard deviation
SOA	Schedule of activities

SRSD	Single Reference Safety Document
SST	Serum separator tube
SUSAR	Suspected unexpected serious adverse reaction
t½	Plasma elimination half life
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TLS	Tumor lysis syndrome
Tmax	Time to maximum plasma concentration
TO	Target occupancy
TSH	Thyroid-stimulating hormone
TTR	Time to tumor response
ULN	Upper limit of normal
UPM	Unit probability mass
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel-Lindau
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Appendix 6. Treatment Recommendations for Symptoms of Avelumab Infusion-Related Reactions

The following treatment recommendations for symptoms of avelumab infusion-related reactions may be modified based on local treatment standards and guidelines, as appropriate.

For Grade 1 Symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

- Decrease the avelumab infusion rate by 50% and monitor closely for any worsening (the total infusion time for avelumab should not exceed 120 minutes).
- Remain at bedside, and monitor patient until recovery from symptoms.

For Grade 2 Symptoms: (Moderate reaction; Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours).

- Stop the avelumab infusion.
- Treat based on emerging symptoms. Treatment may include:
  - Normal saline IV;
  - H1 blockers, such as diphenhydramine 25 to 50 mg IV (or equivalent);
  - H2 blockers, such as ranitidine 50 mg IV (or equivalent);
  - NSAIDs, such as ibuprofen 600 mg (or equivalent);
  - Meperidine 12.5 to 50 mg IV;
  - Corticosteroids, such as hydrocortisone 100 to 500 mg IV (or equivalent);
  - Bronchodilators.
- Remain at bedside, and monitor patient until resolution of symptoms.
- Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.

For Grade 3 or Grade 4 Symptoms: (Severe reaction; Grade 3: prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: life-threatening consequences; urgent intervention indicated).

- Stop the avelumab infusion immediately, and disconnect bag infusion tubing from the patient.
- Begin an IV infusion of normal saline, and treat the patient with one or more of the following:
  - Airway maintenance;
  - Oxygen;
  - Bronchodilators;
  - Epinephrine 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution IM, up to a maximum dose of 0.5 mg;
  - H1 blockers, such as diphenhydramine 25 to 50 mg IV (or equivalent);
  - H2 blockers, such as ranitidine 50 mg IV (or equivalent);
  - Corticosteroids, such as hydrocortisone 100 to 500 mg IV (or equivalent).
- Remain at bedside and monitor patient until recovery from symptoms.
- Avelumab treatment must be permanently discontinued.