CLINICAL PROTOCOL

Renal Cell Carcinoma – Javelin Renal 101

A PHASE 3, MULTINATIONAL, RANDOMIZED, OPEN-LABEL, PARALLEL-ARM STUDY OF AVELUMAB (MSB0010718C) IN COMBINATION WITH AXITINIB (INLYTA®) VERSUS SUNITINIB (SUTENT®) MONOTHERAPY IN THE FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED RENAL CELL CARCINOMA

Compounds:	MSB0010718C, AG-013736, SU011248
Compound Names:	Avelumab, Axitinib, Sunitinib
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Phase:	3

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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 with 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 anti-VEGF monoclonal antibody bevacizumab; and the mTOR inhibitors temsirolimus and everolimus. 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.[2] 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.[3,4]

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.[5,6] Nivolumab, a high-affinity, fully human anti-PD-1 mAb has shown durable tumor responses with an objective response rate (ORR) of about 20% and median progression-free survival (PFS) of about 16 weeks in heavily pretreated aRCC patients.[30,31] 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.[37] 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% 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 a stable disease ≥24 weeks rate of 32% in 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.[32] 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 stable disease (SD), and all these patients (9 out of 10) 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 CTLA-4, showed acceptable safety and encouraging antitumor activity in 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 progression/toxicity. Confirmed ORR 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.[7]

In 2016, nivolumab single agent was approved as 2nd line therapy for aRCC based on the OS benefit reported in the Phase 3 CheckMate 025 trial.[65] In patients with previously treated aRCC, median OS was 25.0 months with nivolumab (95% CI: 21.8 to not estimable) vs 19.6 months (95% CI: 17.6, 23.1) with everolimus (HR= 0.73; 98.5% CI, 0.57 to 0.93; P=0.002) and fewer Grade 3 or 4 AEs occurred with nivolumab than with everolimus.

More recently, data presented at ASCO GU 2017 on the Phase 2 randomized IMmotion 150 trial testing atezolizumab (MPDL3280A) with or without bevacizumab vs sunitinib monotherapy in aRCC, demonstrated a PFS benefit in the PD-L1 positive subpopulation, with a median PFS of 14.7 months (95% CI: 8.2, 25.1) for the combination compared to 7.8 month (95% CI: 3.8, 10.8) for sunitinib monotherapy (HR= 0.64; 95%CI: 0.38, 1.08; P=0.095).[66]

Avelumab (MSB0010718C) is a fully human mAb of the immunoglobulin (Ig) G1 isotype that specifically targets and blocks PD-L1. 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.

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).[20] The anti-tumor 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 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.[8] Toxicities were generally tolerable and manageable, and similar to those observed in clinical trials of axitinib in pre-treated aRCC patients.[9]

The most common adverse events (>20% of patients) reported among 1445 cancer patients receiving single-agent axitinib (regardless of causality) include 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.[18]

The risk of hepatotoxicity is 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.[26] The incidence of hematological toxicity was also low with axitinib in this patient population (eg, Grade 3/4 platelet count decreased and neutrophil count decreased 0.3% for each).[26]

Sunitinib malate (SUTENT®) is an oral multitargeted TKI of stem cell receptor factor (KIT), platelet-derived growth factor-receptors (PDGFRs), VEGFRs, glial cell-line neurotrophic factor receptor (RET), FMS-like tyrosine kinase 3 (FLT3), and colony stimulating factor receptor Type 1 (CSR-1R) that has approved multinationally for the treatment of aRCC. Results from an international randomized Phase 3 trial comparing sunitinib to IFN-α in 750 treatment-naïve metastatic RCC patients demonstrated a statistically significant improvement in PFS and ORR for sunitinib over IFN-α.[23] Median PFS assessed by third-party blinded independent central review (BICR) was significantly longer (11 months) for sunitinib than for IFN-α (5 months) with a hazard ratio of 0.42 (95% CI: 0.32, 0.54) ($p<0.001$). Sunitinib was also associated with a higher ORR than IFN-α by third-party BICR (31% vs. 6% for IFN, $p<0.001$). Median overall survival (OS) was 26.4 months for sunitinib arm and 21.8 months for IFN-α with a hazard ratio of 0.821 (95% CI: 0.673 – 1.001), $p = 0.051$ (log-rank).

Hepatotoxicity is a known risk associated with sunitinib therapy, with Grade 3/4 AST and ALT increased reported in 2% and 3% of treatment-naïve patients with aRCC, respectively.[28] In addition, liver failure and treatment related deaths have been reported in clinical trials (7/2281 [0.3%]) and post-marketing experience with sunitinib.[28] Sunitinib has also been shown to have hematologic toxicity, with Grade 3/4 platelet count decreased 9% and neutrophil count decreased 17% in treatment-naïve patients with aRCC, leading to treatment interruptions, dose reductions and potentially decrease in therapeutic benefit for patients.[28]

In addition rapid-onset of acute renal failure was observed in patients with metastatic renal cell carcinoma when sunitinib was given in combination with tremelimumab.[53]

Since axitinib causes less hepatic and hematologic toxicity than sunitinib, it is considered to be a better partner for pairing with other anti-cancer agents such as avelumab.

[redacted]

Preliminary Safety Data of Avelumab in Combination with Axitinib

The combination of avelumab with axitinib is being tested in study B9991002, a Phase 1b open-label, dose-finding study aiming to evaluate the safety, pharmacokinetics and pharmacodynamics of avelumab in combination with axitinib in patients with previously untreated aRCC. This study was designed to establish the dosing regimen of avelumab and axitinib to be used for any further study with this combination. Study B9991002 is comprised of a dose-finding phase and a dose-expansion phase. The initial doses to be tested (Dose Level 1, [DL1]) were avelumab 10 mg/kg IV Q2W in combination with axitinib 5 mg orally (PO) twice a day (BID) continuously, with 2 lower dose levels to be explored only if the Maximum Tolerated Dose (MTD) was exceeded in DL1.

The dose-finding phase was completed on 12 February 2016. The 6 patients enrolled in this phase of the study completed the 4-week DLT follow-up period as per protocol (corresponding to 2 cycles of 2 weeks each). There was 1 DLT reported: Grade 3 proteinuria, related to axitinib per investigator assessment, which resolved after reducing the dose of axitinib to 3 mg BID. As of 12 February 2016, the AEs recorded in the dose-finding phase were mostly low grade and manageable, with no new unexpected safety signals for the combination when compared to the safety profile of each drug as monotherapy. No patients discontinued the combination due to AEs. Based on these findings, the MTD\RP2D for the combination is avelumab 10 mg/kg IV Q2W and axitinib 5 mg PO BID continuously. Enrollment in the dose-expansion began on 15 February 2016, with a target enrollment of approximately 48 patients. As of 15 August 2016, 46 patients were enrolled and started treatment in this part of the study, and 52 patients were treated overall (6 patients in the dose-finding part and 46 patients in the dose-expansion part).

As of 15 August 2016, the B9991002 study clinical database included data from 47 treated patients (6 patients in the dose-finding part and 41 patients in the dose-expansion part). Overall, the reported TEAEs were mostly low grade and manageable. The most frequent TEAEs (any cause, any grade, experienced by ≥10% patients) were dysphonia (17 patients, 36.2%), fatigue (16 patients, 34.0%), hypertension (14 patients, 29.8%), diarrhea (13 patients, 27.7%), constipation (11 patients, 23.4%), nausea (9 patients, 19.1%), arthralgia, dyspnea, palmar-plantar erythrodysesthesia syndrome, rash (8 patients each, 17.0%), decreased appetite, headache, hypothyroidism, infusion-related reactions (IRR), vomiting (7 patients each, 14.9%), alanine aminotransferase (ALT) increased (6 patients, 12.8%), dizziness, lipase increased, mucosal inflammation and proteinuria (5 patients each, 10.6%). Fifteen (15) patients (31.9%) experienced a Grade 3 TEAE of any cause, including hypertension (5 patients, 10.6%), lipase increased, amylase increased and ALT increased (2 patients each, 4.3%), aspartate aminotransferase (AST) increased, dehydration, fatigue, gamma-glutamyltransferase increased, hyponatremia, hypophosphatemia, IRR, spinal cord compression, mucosal inflammation, pain in extremity, palmar-plantar erythrodysesthesia syndrome, proteinuria, pulmonary embolism, rash, venous thrombosis and urticaria (1 patient each, 2.1%). Three (3) patients (6.4%) experienced a Grade 4 TEAEs of any cause: lipase increased (2 patients, 4.3%) and blood creatine phosphokinase increased (1 patient, 2.1%). One (1) case of Grade 5 TEAE myocarditis (see below for details) was recorded. All Grades 3-5 TEAEs were assessed as related to study treatment by the investigator with the

exception of gamma-glutamyltransferase increased, hyponatremia, spinal cord compression, and pulmonary embolism.

With respect to the potential immune-related AEs, 7 patients (14.9%) developed Grade 1-2 hypothyroidism, 3 patients (6.4%) Grade 1 hyperthyroidism, and 1 patient (2.1%) Grade 1 autoimmune hypothyroidism. In addition, diarrhea (27.7 %, all of Grade 1-2 severity), rash (17% all grades, 2.1% Grade 3), ALT increased (12.8% all grades, 4.3% Grade 3), and AST increased (8.5% all grades, 2.1% Grade 3) were reported. Both hyperthyroidism and hypothyroidism are expected AEs for both avelumab and axitinib. Rash, diarrhea and increased liver enzymes have also been reported with axitinib monotherapy. Medical review of these cases to confirm their immune-related nature is ongoing. In addition, there was one case of fatal myocarditis which was assessed as related to both avelumab and axitinib by the investigator and in which pathology confirmed an immune-mediated cause.

Seven (7) out of 47 treated patients included in the study database discontinued study treatment: 4 patients due to disease progression, 2 patients due to adverse event (fatal myocarditis and Grade 3 creatinine phosphokinase increased, 1 patient each), and 1 due to consent withdrawal.

In conclusion, as of 15 August 2016, the safety profile of the combination appears consistent with that of each study drug as monotherapy. Safety continues to be closely monitored by the B9991002 study team and discussed in regular teleconferences between the study team and the investigators.

In addition, as of 15 August 2016, 36 out of 47 patients in the clinical database were treated for at least 12 weeks prior to the analysis cut-off date and were included in the analysis of best overall response (BOR). The BOR included 1 patient with confirmed CR (2.8%), 15 patients with confirmed PR and 4 patients with unconfirmed PR (52.8%), 9 patients with SD (25.0%), 5 patients with PD (13.9%) and 2 patients not evaluable for response (5.6%; one patient died before the first oncologic assessment due to myocarditis, and another one who never started the combination treatment, discontinued axitinib treatment due to Grade 3 creatinine phosphokinase increased). The objective response rate (including confirmed and unconfirmed responses) is 55.6% (95% CI: 38.1-72.1).

Based on the safety and efficacy data described above, further investigation of avelumab in combination with axitinib in the patient population chosen for this study appears feasible.

Study Objectives:

Primary Objective

- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1) with aRCC.

Secondary Objectives

- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS in the first-line treatment of patients with aRCC unselected for PD-L1 expression.
- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging OS in the first-line treatment of patients with aRCC unselected for PD-L1 expression.
- To evaluate other measures of efficacy of avelumab in combination with axitinib and sunitinib monotherapy in the first-line treatment of aRCC patients.
- To evaluate progression-free survival on next-line of therapy (PFS2).
- To evaluate the overall safety profile of avelumab in combination with axitinib and sunitinib monotherapy in the first-line treatment of aRCC patients.
- To evaluate the time to treatment discontinuation/failure due to toxicity.
- To evaluate the proportion of patients who discontinued treatment due to toxicity.
- To evaluate the population pharmacokinetics of avelumab and axitinib when administered in combination.
- 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 and sunitinib monotherapy.
- To assess the immunogenicity of avelumab when combined with axitinib.
- To evaluate the effects of avelumab in combination with axitinib and sunitinib monotherapy on patient-reported outcomes.

[redacted]

Study Endpoints:

Primary Endpoints

- Progression-Free Survival (PFS) based on Blinded Independent Central Review (BICR) assessment per RECIST v.1.1 for PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1).

- Overall Survival (OS) for PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1).

Secondary Endpoints

- PFS by BICR assessment per RECIST v.1.1 for patients unselected for PD-L1 expression.

- OS for patients unselected for PD-L1 expression.

- Objective Response (OR), Disease Control (DC), Time to Tumor Response (TTR) and Duration of Response (DR) based on BICR assessment and based on Investigator assessment, per RECIST v.1.1.

- Progression-Free Survival (PFS) based on Investigator assessment per RECIST v.1.1.

- Progression-Free Survival on next-line therapy (PFS2).

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 6); vital signs (blood pressure, pulse rate).

- Time to treatment discontinuation/failure due to toxicity.

- Treatment discontinuation due to toxicity.

- PK parameters including trough concentrations (C_{trough}) of avelumab and trough concentrations (C_{trough}) and maximum concentrations (C_{max}) of axitinib.
- 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]).
- Measures of clinical outcome (PFS, OS, OR, DC, TTR, and DR) in biomarker-positive and biomarker-negative subgroups.
- Anti-drug antibodies (ADAs; nAbs) of avelumab when in combination with axitinib.
- Patient-Reported Outcomes (PRO): FACT-Kidney Symptom Index (FKSI-19), EuroQol 5-Dimension (EQ 5D).

[redacted]

Study Design:

This is a Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in which approximately 830 patients, including a minimum of 580 PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1) are planned to be randomized in a 1:1 ratio to receive either avelumab in combination with axitinib or sunitinib monotherapy.

Arm A: avelumab 10 mg/kg IV Q2W in a 6-week cycle + axitinib 5 mg PO BID.

Arm B: sunitinib 50 mg PO QD on Schedule 4/2.

Patients will be stratified according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1) and region (United States vs Canada/Western Europe vs the rest of the world).

Crossover between treatment arms will not be permitted.

Study Treatment:

In Arm A, patients will receive:

- Avelumab as a 1-hour IV infusion Q2W in a 6-week cycle.
- Axitinib PO BID, with or without food, on a continuous dosing schedule.

Treatment with study drugs may continue until confirmed disease progression assessed by BICR (see Section 5.4.4 for further details on treatment continuation after initial evidence of disease progression [PD]), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Study Withdrawal).

Axitinib treatment may be adjusted by dosing interruption with or without dose reduction (Section 5.4.6). Avelumab treatment modification for drug-related toxicities, including irAEs and infusion-related AEs is described in Section 5.4.6.

Axitinib intrapatient dose escalation may occur if relevant criteria are met (see Section 5.4.6.1).

Patients in Arm A 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 confirmed disease progression per BICR assessment (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. At the end of study, Arm A patients who are still deriving clinical benefit from study treatment will be provided with an option for continued study treatment (eg, rollover study).

Patients who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression by BICR assessment 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 who develop disease progression per BICR assessment on study treatment but are otherwise continuing to derive clinical benefit from study treatment (see Section 5.4.4) will be eligible to continue with avelumab combined with axitinib, or single-agent avelumab, or single-agent axitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

In Arm B, patients will receive:

- Sunitinib PO 50 mg QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2 in 6-week cycles).

Treatment with sunitinib may continue until confirmed disease progression assessed by BICR (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Study Withdrawal).

Patients who develop disease progression assessed by BICR on study treatment but are otherwise continuing to derive clinical benefit from study treatment (see Section 5.4.4) will be eligible to continue with sunitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Sunitinib treatment may be adjusted by dosing interruption with or without dose reduction (see Section 5.4.6).

After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression (see Section 7.7).

Statistical Methods:

For some endpoints, analyses will also be performed on the subset of PD-L1+ patients. The associated analyses sets will be a subset of the analyses sets defined below restricted to the PD-L1+ population.

Full Analysis Set

The full analysis set will include all patients who are randomized. Patients will be classified according to the treatment and stratum assigned at randomization. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

Per Protocol Analysis Set

The Per-Protocol Analysis Set is a subset of the Full Analysis Set and will include patients who receive at least 1 dose of study treatment and do not have major protocol deviations expected to impact the primary objective of the study. Major protocol deviations will be pre-specified in the Statistical Analysis Plan (SAP). The Per-Protocol Analysis Set will be used for sensitivity analyses of the primary efficacy endpoints.

Sample Size Determination and Testing Strategy:

The following statistical hypotheses will be tested to address the primary objective:

H_{01}: $HR_{PFS+} \geq 1$ vs. H_{11}: $HR_{PFS+} < 1$

H_{02}: $HR_{OS+} \geq 1$ vs. H_{12}: $HR_{OS+} < 1$

where HR_{PFS+} and HR_{OS+} are the hazard ratios (*Arm A vs. Arm B)* of PFS and OS, respectively, in the PD-L1+ population.

In addition the following statistical hypotheses will be tested to address the secondary objectives:

H_{03}: $HR_{PFS} \geq 1$ vs. H_{13}: $HR_{PFS} < 1$

H_{04}: $HR_{OS} \geq 1$ vs. H_{14}: $HR_{OS} < 1$

where HR_{PFS} and HR_{OS} are the hazard ratios (*Arm A vs. Arm B)* of PFS and OS, respectively, in the 'all comers' population (patients unselected for PD-L1 expression).

Overall type I-error will be maintained at or below 1-sided 0.025 by allocating α=0.004 to the PFS comparison in PD-L1+ patients and by allocating α=0.021 to the OS comparison in the PD-L1+ population. A gatekeeping procedure will be used to allow further testing of PFS and OS in the PD-L1 'all comers' population as described in Figure 2 (Section 9.1). The significance levels for each test will also take into account the group sequential nature of the design (see Section 9.6).

For the primary PFS comparison, 336 PFS events by BICR assessment in the PD-L1+ population will provide 90% power to detect a HR of 0.65 using a 1-sided log rank test at a significance level of 0.004, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-15) β-spending function to determine the non-binding futility boundary.

For the primary OS comparison, 368 OS events in the PD-L1+ population will provide 90% power to detect a hazard ratio of 0.70 using a 1-sided log-rank test at a significance level of 0.021, and a 4-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-3) β-spending function to determine the non-binding futility boundary.

The study will randomize a total of approximately 830 patients, including a minimum 580 PD-L1 positive patients, using a 1:1 randomization, stratified by ECOG PS (0 versus 1) and region (United States vs Canada/Western Europe vs the rest of the world).

The sample size for this study is determined based on the following:

1. The median PFS for patients receiving sunitinib is 11 months[27] and the median PFS for patients receiving avelumab in combination with axitinib is 16.9 months for PD-L1 positive patients and 15.7 months for patients unselected for PD-L1 expression; this corresponds to a hazard ratio (HR) of 0.65 and 0.7, respectively under the exponential model assumption;

2. The median OS for patients receiving sunitinib is 26.4 months[27] and the median OS for patients receiving avelumab in combination with axitinib is 37.7 months for PD-L1 positive patients and 35.2 months for patients unselected for PD-L1 expression; this corresponds to a hazard ratio (HR) of 0.7 and 0.75, respectively under the exponential model assumption;

3. PFS drop-out rate of approximately 15% and OS drop-out rate of approximately 5%;

4. 70% of the randomized patients are PD-L1 positive;

5. Non-uniform patient accrual accomplished over a 21 month period.

The sample size of approximately 830 patients will also allow an assessment of PFS and OS in the 'all comers' population.

If H_{01} is rejected then PFS in the 'all comers' population can be tested and 490 PFS event by BICR assessment will provide 90% power to detect a HR of 0.70 using a 1-sided log rank test at a significance level of 0.004, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.

If either H_{02} or H_{03} are rejected, then OS in the 'all comers' population can be tested at the sum of the significance levels associated with the significant H_{02} and H_{03} tests (see Figure 2, Section 9.1). With 534 OS events, the power is 91% (if both H_{02} and H_{03} are rejected), 90% (if H_{02} is rejected and H_{03} is not rejected) or 74% (if H_{02} is not rejected and H_{03} is rejected) to detect a HR of 0.75 using a 1-sided log rank test at a significance level of 0.025, 0.021 or 0.004, respectively, and a 4-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.

The data cutoff for the primary PFS analysis will occur after the target number of PFS events by BICR assessment in the PD-L1+ population has been reached and the last patient randomized in the study has been followed for at least 12 months after randomization.

The data cutoff for the primary OS analysis will occur after the target number of deaths in the PD-L1+ population has been reached.

The study will be considered positive if the stratified log-rank test for either PFS or OS in the PD-L1+ population is significant at the respective α levels.

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

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 6 weeks = 42 days)					
		Cycle 1			Cycles ≥2		
	≤28 Days Prior to Randomization	Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±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		
ECOG Performance Status[5]	X	X	X	X	X	X	X
Contraception Check[6]	X	X	X	X	X	X	X
Vital Signs[7]	X	X	X	X	X	X	X
Blood Pressure Home Monitoring[8]			X			X	
Laboratory Studies							
Coagulation[9]	X	X (-3 days)	X	X	X	X	X
Hematology[9]	X	X (-3 days)	X	X	X	X	X
Blood Chemistry-Full panel[9]	X	X (-3 days)			X		
Blood Chemistry- Core Panel[10]			X	X		X	X
Thyroid Function Tests[11]	X				X (Cycles 2, 3, then every 2 Cycles		
ACTH[12]	X				X (Cycle 3 then every 2 Cycles)		
HBV, HCV Tests	X	If clinically indicated			If clinically indicated		
Serum/Urine Pregnancy Test[13]	X	X (-3 days)	X	X	X	X	X
Urinalysis[14]	X	If clinically indicated			If clinically indicated		
Cardiac Monitoring							
12-lead ECG[15]	X	X	X	X	If clinically indicated		

Visit Identifiers[1]	**Screening**	**Study Treatment (1 cycle = 6 weeks = 42 days)**					
		Cycle 1			**Cycles ≥2**		
	≤28 Days Prior to Randomization	**Day 1**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 29 (±3 days)**
MUGA Scan or ECHO[29]	X				X (every 2 cycles)		
Cardiac Enzymes[30]	X	X (-3 days)	X	X	X (Cycles 2 and 3 only)	X (Cycles 2 and 3 only)	X (Cycles 2 and 3 only)
Disease Assessments							
Tumor Assessments (including scans)[16]	X	(Q6W [+7 days time window] from randomization up to 18 mos after randomization; Q12W [+7 days time window] thereafter)					
Other Clinical Assessments							
Axitinib/Sunitinib Dosing Compliance Follow-up[17]		X (D5)			As needed based on axitinib/sunitinib dose modifications		
Adverse Events[18]		X	X	X	X	X	X
Concomitant Medications/Treatments[19]	X	X	X	X	X	X	X
FKSI and EuroQol 5-Dimension (EQ-5D)[20]		X			X		
Randomization and Study Treatment[21]							
Avelumab[22] (Arm A only)		X	X	X	X	X	X
Axitinib[22] (Arm A only)			X			X	
Sunitinib[22] (Arm B only)			X			X	
Other Samplings							
Pharmacokinetics for axitinib[23] (Arm A only)		X	X	X			
Pharmacokinetics for avelumab[24] (Arm A only)		X	X	X	X (Cycles 2, 3, 4, 6 then every 2 cycles thereafter up to Cycle 16)		X (Cycles 2, 3, 4 only)
Banked Blood Biospecimens[25]	X	X			X (Cycles 2 and 3 only)		

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 6 weeks = 42 days)					
		Cycle 1			Cycles ≥2		
	≤28 Days Prior to Randomization	Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)
Mandatory Archival FFPE Tumor Tissue[26]	X						
Mandatory Recent FFPE Tumor Tissue Block[27]	X						
Anti-Avelumab Antibodies and Neutralizing Antibodies[28] (Arm A only)		X	X	X	X (Cycles 2, 3, 4, 6 then every 2 Cycles thereafter up to Cycle 16)		X (Cycles 2, 3, 4 only)

Footnotes for Schedule of Activities for SCREENING and STUDY TREATMENT periods

1. **Visit Identifiers:** All assessments should be performed prior to dosing with study treatments 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 pre-dose on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
5. **Physical Examination:** Includes an examination of major body systems and weight (height included at screening only). Weight will be collected before each avelumab infusion. From Cycle 2 onward PE will be performed on Day 1 on each cycle. Additional PE may be performed if clinically indicated. **ECOG PS:** Arm B (Sunitinib Arm): From Cycle 2 onward, Days 15 and 28 ECOG PS will be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. Arm A (this option is applicable only to patients on treatment with single agent axitinib, after they have visited the site every 2 weeks for additional 2 full cycles following avelumab permanent discontinuation): Days 15 and 29 ECOG PS will be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.
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 (see Section 4.3.1 for details on methods allowed). The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if 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. Vital signs will be monitored at screening and on Days 1, 15, and 29 of each cycle during the study. 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/pulse readings will be taken at least 1 hour apart at each clinic visit. Arm B (Sunitinib Arm): From Cycle 2 onward Days 15 and 29 vital signs will be performed and collected at home by the patient and communicated to the site study team during the telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. Arm A (this option is applicable only to patients on treatment with single agent axitinib, after they have visited the site every 2 weeks for additional 2 full cycles following avelumab permanent discontinuation): Days 15 and 29 vital signs will be performed and collected at home by the patient and communicated to the site study team during the telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.
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 once daily (in Arm A before taking the morning dose of axitinib, and in Arm B before taking the daily dose of sunitinib during the 4 weeks of treatment and any time during the day in the 2 weeks off treatment), 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 5.4.6.3).
9.	**Hematology, Blood Chemistry (full panel), and Coagulation**: Required tests are listed in Table 7. Full chemistry panel (required tests are listed in Table 7) is required at screening, on Day 1 of each cycle. May also be performed when clinically indicated. Arm B (Sunitinib Arm): From Cycle 2 onward, Days 15 and 29 laboratory assessments will be performed by local laboratories unless the patient is visiting the site for other reasons. The patient will be instructed to email/fax the results of the laboratories assessments to the site and bring them in at the next visit. Arm A (this option is applicable only to patients on treatment with single agent axitinib, after they have visited the site every 2 weeks for additional 2 full cycles following avelumab permanent discontinuation): Days 15 and 29 laboratory assessments will be performed by local laboratories unless the patient is visiting the site for other reasons. The patient will be instructed to email/fax the results of the laboratories assessments to the site and bring them in at the next visit.
10.	**Blood Chemistry (core panel):** Core chemistry panel (required tests are listed in Table 7) is required on Days 15 and 29 of each cycle.
11.	**Thyroid Function Tests:** Free T4, TSH, tests will be performed at screening, Cycle 2 Day 1, Cycle 3 Day 1, then every 2 cycles thereafter. Additional tests should be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. See Table 7.
12.	**ACTH**: ACTH tests will be performed at screening, Cycle 3 Day 1, then every 2 cycles thereafter. Additional tests should be performed when clinically indicated. See Table 7.
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 on two occasions prior to starting study treatment: once at the start of screening and once at the baseline visit immediately before investigational product administration. During treatment, pregnancy tests (serum or urine test) will also be routinely repeated on Days 1, 15, and 29 of each 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 IRB/ECs or if required by local regulations. Results of the pregnancy test should be evaluable prior to each dosing. (see Section 7.1.1).
14.	**Urinalysis (**Table 7): Required only at Screening. 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 timepoints.

15. **12-Lead ECG**: See Section 7.1.5 for details. All patients require a triplicate ECG measurement at screening. On-treatment ECGs will be performed on Days 1, 15, and 29 of Cycle 1 before avelumab infusion and at the end of infusion in Arm A and before sunitinib drug intake in Arm B. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). If patient experiences a cardiac or neurologic AE (specifically 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. At that time, creatinine kinase (CK) and troponin should be performed in association with clinically indicated ECG assessments. When coinciding with blood sample draws for pharmacokinetics (PK), ECG assessment (as well as CK and troponin, if clinically indicated) should be performed prior to PK blood sample collection, such that the PK blood sample is collected at the nominal time.
16. **Tumor Assessments**: CT or MRI will include chest, abdomen and pelvis (CAP) at all time points. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Premedication prior contrast media administration as per local guidelines is allowed (see Section 5.8.5). Bone scintigraphy/bone scans and brain scans/head CT/MRI are also required at screening. Bone lesion(s) identified at screening by bone scan can be further assessed by CT or MRI as per local practice and subsequently re-assessed by CT or MRI as per tumor assessment schedule. If bone scintigraphy/bone scan is the preferred assessment method for bone lesion(s) as per local practice, re-assessment during study should occur every 12 weeks after randomization. Bone scan will also be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of complete response (CR) confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at screening, otherwise brain will only be evaluated when clinically indicated. The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, at 6 weeks after randomization then every 6 weeks from randomization up to 18 months after randomization and every 12 weeks thereafter until confirmed disease progression by BICR assessment (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD) regardless of initiation of subsequent anti-cancer therapy. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected PD, symptomatic deterioration, etc.). The schedule of assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD. Assessment of response will be made using RECIST v.1.1 and immune-related response criteria (irRECIST) (Nishino 2014, Appendix 3). All radiographic images will be collected and objectively verified by an independent third-party core imaging laboratory (blinded independent central review [BICR]) as described in the Study Manual. After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression. After review of images by BICR is stopped, confirmation of disease progression ≥4 weeks after the PD was first noticed will no longer be required. irRECIST-defined antitumor activity will no longer be collected as per PACL dated 02 September 2019. See Section 7.7 for additional information.
17. **Follow-up for Axitinib/Sunitinib Dosing Compliance**: Follow-up by telephone will be done on Day 5 of the first cycle to confirm patient understanding and compliance with dosing instructions. Axitinib dosing compliance will also be assessed following any dose modification. If needed, patient will be retrained.

18. **Adverse Events**: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. 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 nonserious) 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 administration of the study drug. 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 investigational product, irrespective of any intervening treatment. Arm B (Sunitinib Arm): From Cycle 2 onward, Days 15 and 29 AEs collection will be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. Arm A (this option is applicable only to patients on treatment with single agent axitinib, after they have visited the site every 2 weeks for additional 2 full cycles following avelumab permanent discontinuation): Days 15 and 29 AEs collection will be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. Based on the observed (laboratory tests) and reported findings during the telephone call, the patient might be required to visit the site. The investigator must document in writing the results of the phone call in a specific form and data are to be reported in the CRF.

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). Arm B (Sunitinib Arm): From Cycle 2 onward, Days 15 and 29 concomitant medications collection may be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons. Arm A (this option is applicable only to patients on treatment with single agent axitinib, after they have visited the site every 2 weeks for additional 2 full cycles following avelumab permanent discontinuation): Days 15 and 29 concomitant medications collection may be performed by telephone call (eg, nurse) in a standardized form, unless the patient is visiting the site for other reasons.

20. **Patient-Reported Outcome Questionnaire**: FKSI-19 and EUROQoL 5-Dimension (EQ-5D) are to be administered on Day 1 (on randomization) of Cycle 1, and at Day 1 of each Cycle. PROs are to be administered always prior to any other test/procedure is performed.

21. **Randomization:** An interactive voice and web response system will be used for randomization to a treatment arm. Required information: site and patient identifiers and demographic information. Study treatment should begin within 3 days after randomization.

22. **Study Treatment**: Avelumab will be given as a 1-hour intravenous infusion every 2 weeks in a 6-week cycle. Axitinib will be given orally twice daily PO on a continuous daily dosing schedule. Sunitinib will be given orally 50 mg taken once daily, on a schedule 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

23. **Pharmacokinetics for axitinib:** In Arm A only, PK samples for axitinib (3 mL) will be collected at 2 hours post-dose on Day 1 of Cycle 1 and then at pre-dose and 2 hours post-dose for axitinib on Day 15 and 29 of Cycle 1. Details are outlined in Section 7.3.

24. **Pharmacokinetics for avelumab**: In Arm A only, pre-dose PK samples for avelumab (3.5 mL) will be taken on Day 1, Day 15 and Day 29 of Cycle 1, on Day 1 and Day 29 of Cycles 2-4, Day 1 of Cycle 6 and then every 2 cycles thereafter up to Cycle 16. Pre-dose samples can be taken up to 2 hours prior to the start of avelumab infusion. Details are outlined in Section 7.3.

[redacted]

26. **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 randomization. [redacted] Cytology samples (eg, FFPE cell pellet from Fine Needle Aspiration biopsy) are not acceptable. See Section 6.1.1 and Section 7.5.1.

27. **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. [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. [redacted] See Section 6.1.1 and Section 7.5.1.

28. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab).** In Arm A one blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose at Day 1, Day 15 and Day 29 of Cycle 1, at Day 1 and Day 29 of Cycles 2-4 at Day 1 of Cycle 6, and then every 2 cycles thereafter up to Cycle 16. All samples should be drawn within 2 hours before start of avelumab infusion. All the samples that are positive for ADA may also undergo characterization for Nab. See Section 7.4.

29. **MUGA Scan or ECHO**. For the evaluation of the left ventricular ejection fraction, the technique used at screening will be consistently used throughout the study, in the following assessments.

30. **Cardiac Enzymes**: B-type natriuretic peptide (BNP), troponin, creatine kinase-MB (CK-MB) will be performed at screening and on Cycles 1 2 and 3 on Days 1, 15 and 29. Cardiac enzymes may be also performed when clinically indicated (see also footnote 15). The 99th percentile should be used to define a positive troponin value, and every positive test should be repeated. Arm A: troponin test results must be reviewed by the treating physician before each avelumab administration.

SCHEDULE OF ACTIVITIES FOR END OF TREATMENT AND SHORT-/LONG-TERM FOLLOW-UP Periods

Visit Identifiers[1]	**Post-Treatment**				
	End of Treatment/ Withdrawal)[2]	**Short-Term Follow-Up Visit**[3]			**Long-Term Follow-Up**[3] **every 3 months (±14 days)**
		30 Days (±3 Days) After Last Dose	**60 Days (±3 Days) After Last Dose**	**90 Days (±3 Days) After Last Dose**	
Clinical Assessments					
Physical Examination[4]	X	X	X	X	
ECOG Performance Status	X	X	X	X	X
Contraception Check[5]	X	X	X (Arm B only)		
Vital Signs[6]	X	X	X	X	
Laboratory Studies					
Hematology[7]	X	X	X	X	
Blood Chemistry-Full Panel[8]	X[8]	X[8]	X[8]	X[8]	
Coagulation[7]	X	X	X	X	
Thyroid Function Tests[9]	X	X	X	X	
ACTH[10]	X	X	X	X	
Serum/Urine Pregnancy Test[11]	X	X	X (Arm B only)	X	
Urinalysis[12]	X				
12-lead ECG[13]	X				
MUGA Scan or ECHO[23]	X			X	
Disease Assessments					
Tumor Assessments (including scans)[14]	X (Q6W [+7 days time window] from randomization up to 18 mos after randomization; Q12W [+7 days time window] thereafter)				
Other Clinical Assessments					
Adverse Events[15]	X	X	X	X	
Concomitant Medications/Treatments[16]	X	X	X	X	
New Systemic Anticancer treatment	X	X	X	X	X
Survival Assessment[17]		X	X	X	X

Visit Identifiers[1]	Post-Treatment				
	End of Treatment/ Withdrawal)[2]	Short-Term Follow-Up Visit[3]			Long-Term Follow-Up[3] every 3 months (±14 days)
		30 Days (±3 Days) After Last Dose	60 Days (±3 Days) After Last Dose	90 Days (±3 Days) After Last Dose	
FKSI and EuroQol 5-Dimension (EQ-5D)[18]	X	To be performed in parallel to any tumor assessement by imaging (if any)			
Other Samplings					
Pharmacokinetics[19]		X (Arm A only)			
Banked Blood Biospecimens[20]	X				
De Novo Tumor Biopsy[21]	X				
Anti-Avelumab Antibodies and Neutralizing Antibodies[22]		X (Arm A only)			

Footnotes for Schedule of Activities for End of Treatment and Short-/Long-Term Follow-Up periods

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, ECOG PS, and new systemic anticancer treatment within the long-term follow-up.
4. **Physical Examination:** Includes an examination of major body systems and weight.
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 (see Section 4.3.1 for details on methods allowed). The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. Arm B: contraception requirements/checks should be maintained for at least 49 days after the last sunitinib dose.
6. **Vital Signs:** Vital signs to include blood pressure and 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/pulse readings will be taken at least 1 hour apart at each clinic visit.
7. **Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 7. May also be performed when clinically indicated.
8. **Blood Chemistry**: Full chemistry panel is required at End of Treatment/Withdrawal and during short-term follow-up visits (Days 30 ±3, 60 ±3, 90 ±3 after the last dose). See Table 7.

9. **Thyroid Function Tests**: Free T4 and TSH tests will be performed at End of Treatment/Withdrawal visit and Follow-up visits at 30 ±3, 60 ±3, and 90 ±3 days after the last dose. Additional tests should be performed when clinically indicated. See Table 7.
10. **ACTH Test**: ACTH tests will be performed at End of Treatment/Withdrawal visit and Follow-up visit at 30 ±3, 60 ±3, 90 ±3 days after the last dose. Additional tests should be performed when clinically indicated. See Table 7.
11. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the End of Treatment/Withdrawal visit and at 30 ±3, 60 ±3 (Arm B only). Days Follow-up visit 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 IRB/ECs or if required by local regulations.
12. **Urinalysis:** Required only at the End of Treatment. To be performed as clinically indicated at other timepoints.
13. **12-Lead ECG**: See Section 7.1.5 for details. Triplicate ECG measurements should be performed at end of treatment, and when clinically indicated. Creatinine kinase (CK) and troponin should be performed in association with clinically indicated ECG assessements. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
14. **Tumor Assessments:** CT or MRI will include chest, abdomen and pelvis (CAP) at all time points. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Premedication prior contrast media administration as per local guidelines is allowed (see Section 5.8.5). Bone scintigraphy/bone scans and brain scans/head CT/MRI are also required at screening. Bone lesion(s) identified at screening by bone scan can be further assessed by CT or MRI as per local practice and subsequently re-assessed by CT or MRI as per tumor assessment schedule. If bone scintigraphy/bone scan is the preferred assessment method for bone lesion(s) as per local practice, re-assessment during study should occur every 12 weeks after randomization. Bone scan will also be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of complete response (CR) confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at screening, otherwise brain will only be evaluated when clinically indicated. The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, at 6 weeks from randomization, then every 6 weeks up to 18 months after randomization and every 12 weeks thereafter until confirmed disease progression by BICR assessment regardless of initiation of subsequent anti-cancer therapy. The schedule of assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected PD, symptomatic deterioration, etc.). CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD. Assessment of response will be made using RECIST v.1.1 [redacted]. All radiographic images will be collected and objectively verified by an independent third-party core imaging laboratory (blinded independent central review [BICR]) as described in the Study Manual. After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression. After review of images by BICR is stopped, confirmation of disease progression ≥4 weeks after the PD was first noticed will no longer be required. irRECIST-defined antitumor activity will no longer be collected as per PACL dated 02 September 2019. See Section 7.7 for additional information.

15. **Adverse Events:** Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. 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 nonserious) 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 administration of the study drug. 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 investigational product, 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. **Survival Assessment**: 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. Information will be collected by telephone call unless the patient is visiting the site for other reasons. The Sponsor will request an "ad hoc" survival update prior to each protocol-specified interim analysis and final analysis. The investigator or designee must make every effort to collect the patient's status through contacting the patient or a relative or their usual health care provider by telephone or other allowed methods. These contact attempts should be documented in the patient's medical record.
18. **Patient-Reported Outcome Questionnaire**: FKSI-19 and EUROQoL 5-Dimension (EQ-5D) are to be administered at the End of Treatment/Withdrawal visit. PROs should be administered prior to other End of Treatment/Withdrawal measures. Beyond End of Treatment (ie, follow-up period), PRO assessments will be collected at the same time a tumor assessment is performed.
19. **Pharmacokinetics**: In Arm A, PK blood samples for avelumab (3.5 mL) will be taken 1 month after end of avelumab treatment. Details are outlined in Section 7.3.
[redacted]
21. ***De Novo* Tumor Biopsy:** A *de novo* (ie, fresh biopsy) tumor sample should also be collected at End of Treatment/Withdrawal visit, 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), [redacted] should be submitted to the Central Laboratory. See Section 7.5.1.
22. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** In Arm A**,** one blood sample (3.5 mL) for anti-avelumab antibodies (and simultaneous pharmacokinetic draws for measurement of avelumab) will be collected at 30 days after the end of avelumab treatment. All the samples that are positive for ADA may also undergo characterization for Nab. See Section 7.4.
23. **MUGA Scan or ECHO.** For the evaluation of the left ventricular ejection fraction, the technique used at screening will be consistently used throughout the study, in the following assessments.

SCHEDULE OF ACTIVITIES FOR STUDY TREATMENT, END OF TREATMENT AND FOLLOW-UP PERIODS POST IA3 CUT OFF DATE (28-APR-2020)

	On Treatment (1 cycle = 6 weeks = 42 days)			Post-Treatment				
Visit Identifiers[1]	Cycles ≥2			End of Treatment/ Withdrawal[2]	Short-Term Follow-Up Visit[3]			Long-Term Follow-Up[3]
	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)		30 Days (±3 Days) After Last Dose	60 Days (±3 Days) After Last Dose	90 Days (±3 Days) After Last Dose	Every 3 months (±14 days)
Clinical Assessments								
Informed Consent (Re-consent)[4]	X							
Weight[5]	X	X	X					
ECOG Performance Status[6]	X (in parallel to any tumor assessment by imaging)			X	X (in parallel to any tumor assessment by imaging, if any)			
Contraception Check[7]	X		X	X	X	X (Arm B only)		
Vital Signs[8]	X			X	X	X	X	
Laboratory Studies								
Hematology[9]	X			X	X	X	X	
Blood Chemistry[9]	X			X	X	X	X	
Thyroid Function Tests[10]	X (every 2 odd cycles)			X			X	
ACTH[11]	X (every 2 odd cycles)			X			X	
Serum/Urine Pregnancy Test[12]	X		X	X	X	X (Arm B only)		

	On Treatment (1 cycle = 6 weeks = 42 days)			Post-Treatment				
Visit Identifiers[1]	Cycles ≥2			End of Treatment/ Withdrawal[2]	Short-Term Follow-Up Visit[3]			Long-Term Follow-Up[3]
	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)		30 Days (±3 Days) After Last Dose	60 Days (±3 Days) After Last Dose	90 Days (±3 Days) After Last Dose	Every 3 months (±14 days)
Cardiac Monitoring								
MUGA Scan or ECHO[13]	X (As per institutional practice)							
Disease Assessments								
Tumor Assessments (including scans)[14]	X (Q6W [+7 days time window] from randomization up to 18 mos after randomization; Q12W [+7 days time window] thereafter)			X				
Other Clinical Assessments								
Adverse Events[15]	←==========→			X	X	X	X	
Concomitant Medications/Treatments[16]	←==========→			X	X	X	X	
FKSI and EuroQol 5-Dimension (EQ-5D)[17]	X			X	X (in parallel to any tumor assessment by imaging, if any)			
Study Treatment Administration								
Avelumab[18] (Arm A only)	X	X	X					
Axitinib[18] (Arm A only)	X							
Sunitinib[18] (Arm B only)	X							
Other Samplings								
[redacted]				[redacted]				
De Novo Tumor Biopsy[20]				X				
New Anticancer Treatments[21]								X
Survival[21]								X

Footnotes for Schedule of Activities for STUDY TREATMENT, END OF TREATMENT and FOLLOW-UP periods POST IA3
1. **Visit Identifiers:** During treatment, all assessments should be performed prior to dosing with study treatment/s unless otherwise indicated. 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 through 90 days after the last dose of investigational product or until the time of initiation of new anticancer treatment whichever comes first. During the Long-Term Follow-Up until the end of the study, all patients will be followed every 3 months for survival and new systemic anticancer treatment will be collected.
4. **Informed Consent**: Re-consent must be obtained as applicable.
5. **Weight:** To be collected before each avelumab infusion. See Section 5.4.1 for details on avelumab dose calculation.
6. **ECOG PS:** During treatment, ECOG PS should be performed in parallel to any tumor assessment by imaging.
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 (see Section 4.3.1 for details on methods allowed). The investigator or his or her designee will discuss with the patient the need to use 1 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception method is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. For female patients of childbearing potential, Day 29 contraception check will be collected by telephone call. Arm B: contraception requirements/checks should be maintained for at least 49 days after the last sunitinib dose.
8. **Vital Signs:** Vital signs include blood pressure and 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/pulse readings will be taken at least 1 hour apart at each clinic visit.
9. **Hematology, Blood Chemistry:** (see Table 8): Additional assessments to be performed when clinically indicated.
10. **Thyroid Function Tests:** (see Table 8): Additional tests to be performed when clinically indicated. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state.
11. **ACTH:** Additional tests to be performed when clinically indicated.
12. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, during treatment, pregnancy tests (serum or urine test) will be routinely repeated on Days 1 and 29 of each treatment cycle or whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Day 29 pregnacy test result will be collected by telephone call. Additional pregnancy tests may also be undertaken if requested by IRB/ECs or if required by local regulations (for details see Section 7.1.1).
13. **MUGA Scan or ECHO:** On treatment to be performed as per institutional practice. For the evaluation of the left ventricular ejection fraction (LVEF), the technique used at screening should be consistently used throughout the study, in the following assessments.
14. **Tumor Assessments:** CT or MRI will include chest, abdomen and pelvis (CAP) at all time points. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Premedication prior contrast media administration as per local guidelines is allowed (see Section 5.8.5). Bone scintigraphy/bone scans and brain scans/head CT/MRI are required on treatment if bone and/or brain lesions are identified at screening. Bone lesion(s) identified at screening by bone scan can be further assessed by CT or MRI as per local practice and subsequently re-assessed by CT or MRI as per tumor assessment schedule. If bone scintigraphy/bone scan is the preferred assessment method for bone lesion(s) identified at screening, re-assessment during study should occur every 12 weeks after randomization. Bone scan will also be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of complete response (CR) confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at screening, otherwise brain will only be evaluated when clinically indicated. The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. During treatment, anti-tumor activity will be assessed through radiological tumor assessments conducted every 6 weeks from randomization up to 18 months after

randomization and every 12 weeks thereafter until disease progression by investigator assessment or initiation of subsequent anti-cancer therapy, whichever is earlier (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD). Further imaging assessments may be performed at any time if clinically indicated (eg, suspected PD, symptomatic deterioration, etc.). The schedule of assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. Assessment of response will be made using RECIST v.1.1. See Section 7.7 for additional information.
15. **Adverse Events**: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. 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 nonserious) 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 administration of the study drug. 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 investigational product, irrespective of any intervening treatment.
16. **Concomitant Medications/Treatments**: Concomitant medications and treatments should 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. **Patient-Reported Outcome Questionnaire**: FKSI-19 and EUROQoL 5-Dimension (EQ-5D). PROs are to be administered always prior to any other test/procedure is performed.
18. **Study Treatment**: Avelumab will be given as a 1-hour intravenous infusion every 2 weeks in a 6-week cycle. Axitinib will be given orally twice daily PO on a continuous daily dosing schedule. Sunitinib will be given orally 50 mg taken once daily, on a schedule 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).
[redacted]
20. ***De Novo* Tumor Biopsy:** A *de novo* (ie, fresh biopsy) tumor sample should be collected 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), [redacted] should be submitted to the Central Laboratory. See Section 7.5.1.
21. **New Anticancer Treatments/Survival Assessment**: 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. Information will be collected by telephone call unless the patient is visiting the site for other reasons. The Sponsor will request an "ad hoc" survival update prior to each protocol-specified interim analysis and final analysis. The investigator or designee must make every effort to collect patient's status through contacting the patient or a relative or their usual health care provider by telephone or other allowed methods. These contact attempts should be documented in the patient's medical record.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Previously Untreated Advanced Renal Cell Carcinoma (aRCC).

The mechanisms of action of each investigational product are described in Sections 1.2.2.1 and Section 1.2.2.2.

1.2. Background and Rationale

1.2.1. Renal Cell Carcinoma

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 with 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 (Type I and II), chromophobe, collecting duct, and unclassified RCC.[12] Four RCC predisposing genes have been identified – *MET* protooncogene, von Hippel-Lindau (*VHL*) tumor suppressor gene, fumarate hydratase (*FH*) tumor suppressor gene, 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).[13]

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.[14]

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 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.[14-17]

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

One of the investigational products 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.[36] For complete details of the in vitro and nonclinical studies, refer to avelumab investigator's brochure (IB).[19]

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 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, which is 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).

[redacted]

[redacted]

[redacted]

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab IB. The reference safety information (RSI) can be found in tabular format in Section 6.2 of the avelumab IB.[19]

1.2.2.2. Axitinib (INLYTA®, AG-013736)

One of the investigational products 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 after failure of one prior systemic therapy (actual indication varies according to region/country).[20]

Axitinib is an adenosine triphosphate (ATP)-competitive inhibitor that binds to the unphosphorylated (non-activated) "DFG-out" conformation of the catalytic domain of a receptor tyrosine kinase. In enzymatic assays, axitinib was found to be highly potent (K_i = 28 picomolar) against the kinase activity of juxta-membrane (JM) domain containing human VEGFR 2 recombinant protein.[18] 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 anti-tumor efficacy including marked cytoreductive anti-tumor 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 advanced RCC (99% clear cell) whose disease had progressed on or after treatment with 1 prior systemic therapy, including sunitinib-, bevacizumab-, temsirolimus-, or cytokine-containing regimens were randomized to receive axitinib (N=361) or sorafenib (N=362). There was a statistically significant advantage for axitinib over sorafenib for the primary PFS endpoint, 6.7 months (95% CI: 6.3, 8.6) vs 4.7 months (95% CI: 4.6, 5.6), respectively ($p < 0.0001$). 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, respectively. The ORR was 19.4% (95% CI: 15.4, 23.9) for axitinib and 9.4% (95% CI: 6.6, 12.9) for sorafenib. The most common (≥20%) adverse reactions observed in this study following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.[9]

In 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), respectively, with stratified hazard ratio 0.77 (95% CI: 0.56, 1.05). 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.[8] 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.[8]

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.

Following oral administration, axitinib is rapidly absorbed (median Tmax 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 pharmacokinetics within the 1-mg to 20-mg dose range. The mean absolute bioavailability of axitinib after an oral 5 mg dose is 58%. Axitinib can 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 single reference safety document (SRSD), which for this study is the axitinib IB. The RSI can be found in tabular format in Section 7.8 of the axitinib IB.[18]

1.2.2.3. Sunitinib Malate (SUTENT®, SU011248)

One of the investigational products in the present clinical trial is sunitinib malate (SUTENT®), which is an oral, multitargeted TKI of KIT, PDGFRs, VEGFRs, RET, and FLT3, approved multinationally for the treatment of aRCC.

The safety and efficacy of sunitinib were evaluated in an international, randomized Phase 3 trial comparing sunitinib to IFN-α in 750 treatment-naïve patients with clear-cell mRCC.[23] Patients were randomized 1:1 to receive sunitinib 50 mg BID schedule 4/2 (ie, 4 weeks on treatment followed by 2 weeks off treatment) in 6-week cycles or IFN-α 9MU via subcutaneous (SC) injection 3 times a week in 6-week cycles. The primary endpoint was PFS. Secondary endpoints included ORR, OS, and adverse events. Baseline characteristics were well balanced and included pooled median age of 60 years and prior nephrectomy in 90% of patients. Median PFS assessed by third-party BICR was significantly longer (11 months) for sunitinib than for IFN-α (5 months) with a hazard ratio of 0.42 (95% CI 0.32, 0.54) ($p<0.001$). The results were similar in the analysis using the investigator's assessment: 11 months vs. 4 months, with a hazard ratio of 0.42 (95% CI, 0.33 to 0.52; $p<0.001$). Sunitinib was also associated with a higher ORR than IFN-α by BICR (31% vs. 6% for IFN-α, $p<0.001$). Median OS was 26.4 months for the sunitinib arm, and 21.8 for IFN-α (hazard ratio for death, 0.821, 95% CI. 0.673 1.001, $p = 0.051$ (log-rank). These results demonstrated a statistically significant improvement in PFS and ORR for sunitinib over IFN-α in the first-line treatment of mRCC patients. Eight percent of patients withdrew from the study due to adverse event on the sunitinib arm vs. 13% on the IFN-α arm. The most common (≥20%) adverse reactions observed in this study following treatment with sunitinib were diarrhea, fatigue, nausea, stomatitis, vomiting, hypertension, hand-foot syndrome, and mucosal inflammation.[23]

Overall, the adverse events reported for sunitinib in clinical studies have been considered tolerable and manageable. The most common adverse events, regardless of causality, reported from 9955 patients with solid malignant tumors treated with single-agent sunitinib in a variety of clinical trials included diarrhea (51.5%), fatigue (47.8%), nausea (42.3%),

decreased appetite (38.3%), vomiting (33.6%), palmar-plantar erythrodysaesthesia syndrome (28.5%), hypertension (27.3%), stomatitis (25.0%), dysgeusia (25.8%), and mucosal inflammation (25.1%).

In adults, repeated dosing studies over a range of 25-100 mg daily doses followed by off-treatment periods have identified a 50 mg dose on the Schedule 4/2 (4 weeks of therapy followed by a 2-week off period) as a tolerable, dose dense regimen.[21,22] Steady state levels of sunitinib and its active metabolite SU012662 are reached 7-10 days after repeated daily dosing. Drug accumulation with repeated 4- or 6-week cycles has not been observed. No dose-dependent changes in Tmax or t1/2 have been observed. Sunitinib is metabolized primarily by the cytochrome P450 enzyme, 3A4 (CYP3A4). The terminal elimination half-lives of sunitinib and SU012662 are approximately 40 hours and 80 hours, respectively.

Complete information for sunitinib may be found in the single reference safety document (SRSD), which for this study is the sunitinib IB. The reference safety information (RSI) can be found in tabular format in Section 7.8 of the sunitinib IB.[29]

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.[10,11]

Until 2005, IFN-α and high-dose IL-2 therapies were the standards of care for patients with aRCC, albeit with modest efficacy. Since then, the increasing knowledge of the tumor biology, namely of the role of tumor angiogenesis and its mediators, led to the 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 anti-VEGF monoclonal antibody bevacizumab; and the mTOR inhibitors temsirolimus and everolimus. 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.[2] 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-PD1 and anti-PD-L1 antibodies in recent years. Upregulation of PD-1 receptor on TILs, and its ligand PD-L1 on tumors, are associated with more aggressive disease and poor prognosis.[3,4]

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.[5,6] Nivolumab, a high-affinity, fully human anti-PD-1 monoclonal antibody (mAb) has shown durable tumor response with ORR of about 20% and median PFS of about 16 weeks in heavily pretreated aRCC patients.[30,31] 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 ASCO 2014 annual meeting.[37] [redacted] sunitinib (50 mg, 4 wks on, 2 wks 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 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. [redacted] Results from the combination of bevacizumab 15 mg/kg Q3W with MPDL3280A were also presented by McDermott et al at the ESMO 2014 annual meeting.[32] Data were limited, but in previously untreated aRCC patients, there were 4/10 (40%) partial responses (PRs). Five additional patients had a best response of stable disease, and all responding patients (9 out of 10) were still on treatment at the time of analysis. These data, although preliminary, demonstrate the benefit of combining a 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 CTLA-4, showed acceptable safety and encouraging antitumor activity in 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 progression/toxicity. Confirmed ORR 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.[7]

In 2016, nivolumab single agent was approved as 2nd line therapy for aRCC based on the OS benefit reported in the Phase 3 CheckMate 025 trial.[65] In patients with previously treated aRCC, median OS was 25.0 months with nivolumab (95% CI: 21.8 to not estimable) vs 19.6 months (95% CI: 17.6, 23.1) with everolimus (HR= 0.73; 98.5% CI, 0.57 to 0.93; P=0.002), and fewer Grade 3 or 4 AEs occurred with nivolumab than with everolimus.

More recently, data presented at ASCO GU 2017 on the Phase 2 randomized IMmotion 150 trial testing atezolizumab (MPDL3280A) with or without bevacizumab vs sunitinib monotherapy in aRCC, demonstrated a PFS benefit in the PD-L1 positive subpopulation, with a median PFS of 14.7 months (95% CI: 8.2, 25.1) for the combination compared to 7.8 month (95% CI: 3.8, 10.8) for sunitinib monotherapy (HR= 0.64; 95% CI: 0.38, 1.08; P=0.095).[66]

Avelumab is a fully human mAb of the IgG1 isotype that specifically targets and blocks PD-L1.[33] 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 single agent or in combination with chemotherapy, tyrosine kinase inhibitors, or other immune-modulating agents.

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).[20] Anti-tumor 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.[8] 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.[9]

The most common adverse events (>20% of patients) reported among 1445 cancer patients receiving single-agent axitinib (regardless of causality) include 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.[18]

Hepatotoxicity is a known risk associated with sunitinib therapy, with Grade 3/4 AST and ALT increased reported in 2% and 3% of treatment-naïve patients with aRCC, respectively.[28] In addition, liver failure and treatment related deaths have been reported in clinical trials (7/2281 [0.3%]) and post-marketing experience with sunitinib.[28] Sunitinib has also been shown to have hematologic toxicity, with Grade 3/4 platelet count decreased 9% and neutrophil count decreased 17% in treatment-naïve patients with aRCC, leading to treatment interruptions, dose reductions and potentially decrease in therapeutic benefit for patients.[28] In addition rapid-onset of acute renal failure was observed in patients with metastatic renal cell carcinoma when sunitinib was given in combination with tremelimumab.[53]

The risk of hepatotoxicity is low in patients with aRCC with axitinib, with an overall rate of Grade 3/4 ALT or AST increased <0.6% for each.[26] The incidence of hematological toxicity was also low with axitinib in this patient population (eg, Grade 3/4 platelet count decreased and neutrophil count decreased 0.3% for each.[26]

Since axitinib causes less hepatic and hematologic toxicity than sunitinib, it is considered to be a better partner for pairing with other anti-cancer agents such as avelumab.

[redacted]

[redacted]

Preliminary Safety Data of Avelumab in Combination with Axitinib

The combination of avelumab with axitinib is being tested in study B9991002, a Phase 1b open-label, dose-finding study aiming to evaluate the safety, pharmacokinetics and pharmacodynamics of avelumab in combination with axitinib in patients with previously untreated aRCC. This study was designed to establish the dosing regimen of avelumab and axitinib to be used for any further study with this combination. Study B9991002 is comprised of a dose-finding phase and a dose-expansion phase. The initial doses to be tested (Dose Level 1, [DL1]) were avelumab 10 mg/kg IV Q2W in combination with axitinib 5 mg orally (PO) twice a day (BID) continuously, with 2 lower dose levels to be explored only if the Maximum Tolerated Dose (MTD) was exceeded in DL1.

The dose-finding phase was completed on 12 February 2016. The 6 patients enrolled in this phase of the study completed the 4-week DLT follow-up period as per protocol (corresponding to 2 cycles of 2 weeks each). There was 1 DLT reported: Grade 3 proteinuria, related to axitinib per investigator assessment, which resolved after reducing the dose of axitinib to 3 mg BID. As of 12 February 2016, the AEs recorded in the dose-finding phase were mostly low grade and manageable, with no new unexpected safety signals for the combination when compared to the safety profile of each drug as monotherapy. No patients discontinued the combination due to AEs. Based on these findings, the MTD\RP2D for the combination is avelumab 10 mg/kg IV Q2W and axitinib 5 mg PO BID continuously. Enrollment in the dose-expansion began on 15 February 2016, with a target enrollment of approximately 48 patients. As of 15 August 2016, 46 patients were enrolled and started treatment in this part of the study, and 52 patients were treated overall (6 patients in the dose-finding part and 46 patients in the dose-expansion part).

As of 15 August 2016, the B9991002 study clinical database included data from 47 treated patients (6 patients in the dose-finding part and 41 patients in the dose-expansion part). Overall, the reported TEAEs were mostly low grade and manageable. The most frequent TEAEs (any cause, any grade, experienced by ≥10% patients) were dysphonia (17 patients, 36.2%), fatigue (16 patients, 34.0%), hypertension (14 patients, 29.8%), diarrhea (13 patients, 27.7%), constipation (11 patients, 23.4%), nausea (9 patients, 19.1%), arthralgia, dyspnea, palmar-plantar erythrodysesthesia syndrome, rash (8 patients each, 17.0%), decreased appetite, headache, hypothyroidism, infusion-related reactions (IRR), vomiting (7 patients each, 14.9%), alanine aminotransferase (ALT) increased (6 patients, 12.8%), dizziness, lipase increased, mucosal inflammation and proteinuria (5 patients each, 10.6%). Fifteen (15) patients (31.9%) experienced a Grade 3 TEAE of any cause, including hypertension (5 patients, 10.6%), lipase increased, amylase increased and ALT increased (2 patients each, 4.3%), aspartate aminotransferase (AST) increased, dehydration, fatigue, gamma-glutamyltransferase increased, hyponatremia, hypophosphatemia, IRR, spinal cord compression, mucosal inflammation, pain in extremity, palmar-plantar erythrodysesthesia syndrome, proteinuria, pulmonary embolism, rash, venous thrombosis and urticaria (1 patient each, 2.1%). Three (3) patients (6.4%) experienced a Grade 4 TEAEs of any cause: lipase

increased (2 patients, 4.3%) and blood creatine phosphokinase increased (1 patient, 2.1%). One (1) case of Grade 5 TEAE myocarditis (see below for details) was recorded. All Grades 3-5 TEAEs were assessed as related to study treatment by the investigator with the exception of gamma-glutamyltransferase increased, hyponatremia, spinal cord compression, and pulmonary embolism.

With respect to the potential immune-related AEs, 7 patients (14.9%) developed Grade 1-2 hypothyroidism, 3 patients (6.4%) Grade 1 hyperthyroidism, and 1 patient (2.1%) Grade 1 autoimmune hypothyroidism. In addition, diarrhea (27.7 %, all of Grade 1-2 severity), rash (17% all grades, 2.1% Grade 3), ALT increased (12.8% all grades, 4.3% Grade 3), and AST increased (8.5% all grades, 2.1% Grade 3) were reported. Both hyperthyroidism and hypothyroidism are expected AEs for both avelumab and axitinib. Rash, diarrhea and increased liver enzymes have also been reported with axitinib monotherapy. Medical review of these cases to confirm their immune-related nature is ongoing. In addition, there was one case of fatal myocarditis which was assessed as related to both avelumab and axitinib by the investigator and in which pathology confirmed an immune-mediated cause.

Seven (7) out of 47 treated patients included in the study database discontinued study treatment: 4 patients due to disease progression, 2 patients due to adverse event (fatal myocarditis and Grade 3 creatinine phosphokinase increased, 1 patient each), and 1 due to consent withdrawal.

In conclusion, as of 15 August 2016, the safety profile of the combination appears consistent with that of each study drug as monotherapy. Safety continues to be closely monitored by the B9991002 study team and discussed in regular teleconferences between the study team and the investigators.

In addition, as of 15 August 2016, 36 out of 47 patients in the clinical database were treated for at least 12 weeks prior to the analysis cut-off date and were included in the analysis of best overall response (BOR). The BOR included 1 patient with confirmed CR (2.8%), 15 patients with confirmed PR and 4 patients with unconfirmed PR (52.8%), 9 patients with SD (25.0%), 5 patients with PD (13.9%) and 2 patients not evaluable for response (5.6%; one patient died before the first oncologic assessment due to myocarditis, and another one who

never started the combination treatment, discontinued axitinib treatment due to Grade 3 creatinine phosphokinase increased). The objective response rate (including confirmed and unconfirmed responses) is 55.6% (95% CI: 38.1-72.1).

Based on the safety and efficacy data described above, further investigation of avelumab in combination with axitinib in the patient population chosen for this study appears feasible.

1.2.4. Rationale for Avelumab, Axitinib, and Sunitinib Starting Dosing Regimens

1.2.4.1. Avelumab and Axitinib Starting Dosing Regimens

In Arm A, avelumab will be given in combination with axitinib. The avelumab dosing regimen will be 10 mg/kg administered as a 1-hour intravenous (IV) infusion every 2 weeks (Q2W, 3 doses in a 6-week cycle).

The axitinib starting dosing regimen will be 5 mg administrated orally (PO) twice daily (BID) with or without food.

These dosing regimens have been proven to be safe and tolerable in study B9991002 (see Section 1.2.3).

1.2.4.2. Sunitinib Starting Dosing Regimen

In Arm B, the sunitinib dose will be 50 mg PO once daily (QD) continuously for 4 consecutive weeks followed by a 2-week off-treatment period (Schedule 4/2 in 6-week cycles) with or without food. This dose schedule has proven to be safe and efficacious in patients with aRCC and has been approved by regulatory authorities worldwide.

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.

Blocking the PD-1/PD-L1 pathway by agents binding either PD-1 or PD-L1 (anti-PD1 mAB or anti-PDL1 mAB) is a novel immunotherapeutic approach for aRCC, and anti-PD1 and anti-PDL1 agents have shown single-agent efficacy in patients whose disease has progressed following VEGF pathway inhibitor therapy. Furthermore, anti-PD1/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.[5,32,37] 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.[51,52] Therefore, the addition of axitinib, which is a standard therapy for patients with RCC, might lead to synergistic activity with avelumab in treating patients with aRCC.

Thus far, avelumab has demonstrated a manageable safety profile and significant anti-tumor activity in various tumor types, including aRCC (see Section 1.2.2.1).[19]

Axitinib is approved multinationally for the treatment of aRCC after failure of one prior systemic therapy. Furthermore, axitinib has been studied as first line treatment in a Phase 3 trial and in this setting the safety profile is comparable to the ones experienced by second line patients.[8,9] Overall, the adverse events reported for axitinib in clinical studies is considered tolerable and manageable, and are well characterized (see Section 1.2.2.2). Moreover, since axitinib causes less hepatic and hematologic toxicity than sunitinib, it is considered to be a better partner for pairing with other anti-cancer agents such as avelumab.

Given the occurrence in the early phases of treatment of the 2 cases described above, the study plans to monitor patients at regular intervals as described in the Schedule of Activities, including MUGA/Echocardiogram, ECG, BNP, troponin and CK-MB monitoring. Moreover guidelines about the management of suspect or confirmed cases of myocarditis and relevant avelumab management instructions have been added to Table 6.

As to the anti-tumor activity of the combination, preliminary data with the combination are encouraging as 1 confirmed CR (2.6%), 19 PRs overall (15 confirmed PRs) (52.8%), 9 SDs (25%) have been reported for a objective response rate (confirmed and unconfirmed) of 55.6% (95% CI: 38.1-72.1).

As for the control arm of the study B9991003, sunitinib is approved multinationally for the first line treatment of aRCC patients. Overall, the adverse events reported for sunitinib in clinical studies are well characterized and considered tolerable and manageable. The choice of sunitinib as control treatment for the study appears therefore justified.

In conclusion, the proposed scientific rationale and the preliminary benefit-risk profile of avelumab plus axitinib observed in study B9991002 support the further investigation of the combination in the patient population chosen for this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS or OS in the first-line treatment of PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1) with aRCC.

Secondary Objectives

- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging PFS in the first-line treatment of patients with aRCC unselected for PD-L1 expression.
- To demonstrate that avelumab in combination with axitinib is superior to sunitinib monotherapy in prolonging OS in the first-line treatment of patients with aRCC unselected for PD-L1 expression.
- To evaluate other measures of efficacy of avelumab in combination with axitinib and sunitinib monotherapy in the first-line treatment of aRCC patients.
- To evaluate progression-free survival on next-line of therapy (PFS2).
- To evaluate the overall safety profile of avelumab in combination with axitinib and sunitinib monotherapy in the first-line treatment of aRCC patients.
- To evaluate the population pharmacokinetics of avelumab and axitinib when administered in combination.
- To evaluate the time to treatment discontinuation/failure due to toxicity.
- To evaluate the proportion of patients who discontinued treatment due to toxicity.
- 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 and sunitinib monotherapy.
- To assess the immunogenicity of avelumab when combined with axitinib.
- To evaluate the effects of avelumab in combination with axitinib and sunitinib monotherapy on patient-reported outcomes.

[redacted]

[redacted]

[redacted]

2.2. Endpoints

Primary Endpoints

- Progression-Free Survival (PFS) based on Blinded Independent Central Review (BICR) assessment per RECIST v.1.1[34] for PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1).

- Overall Survival (OS) for PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1).

Secondary Endpoints

- PFS by BICR assessment per RECIST v.1.1 for patients unselected for PD-L1 expression

- OS for patients unselected for PD-L1 expression.

- Objective Response (OR), Disease Control (DC), Time to Tumor Response (TTR) and Duration of Response (DR) based on BICR assessment and based on Investigator assessment, per RECIST v.1.1.[34]

- Progression-Free Survival (PFS) based on Investigator assessment per RECIST v.1.1.[34]

- Progression-Free Survival on next-line therapy (PFS2).

- Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 6); vital signs (blood pressure, pulse rate).

- Time to treatment discontinuation/failure due to toxicity).

- Treatment discontinuation due to toxicity.

- PK parameters including trough concentrations (C_{trough}) of avelumab and trough concentrations (C_{trough}) and maximum concentrations (C_{max}) of axitinib.
- 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]).
- Measures of clinical outcome (PFS, OS, OR, DC, TTR, and DR) in biomarker-positive and biomarker-negative subgroups.
- Anti-drug antibodies (ADAs; nAbs) of avelumab when in combination with axitinib.
- Patient-Reported Outcomes (PRO): FACT-Kidney Symptom Index (FKSI-19), EuroQol 5-Dimension (EQ 5D).

[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 3, multinational, multicenter, randomized (1:1), open-label, parallel 2-arm study in which approximately 830 patients including a minimum of 580 PD-L1 positive patients (patient population prospectively defined as noted in Section 7.5.1) are planned to be randomized to receive either avelumab in combination with axitinib or sunitinib monotherapy.

Arm A: avelumab 10 mg/kg IV Q2W in a 6-week cycle + axitinib 5 mg PO BID.

Arm B: sunitinib 50 mg PO QD on Schedule 4/2.

Patients will be stratified according to ECOG PS (0 vs. 1) and region (United States vs Canada/Western Europe vs the rest of the world).

Crossover between treatment arms will not be permitted.

3.1.1. Study Treatment

In Arm A, patients will receive:

- Avelumab as a 1-hour IV infusion Q2W in a 6-week cycle.
- Axitinib PO BID, with or without food, on a continuous dosing schedule.

Treatment with study drugs may continue until confirmed disease progression assessed by BICR (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Study Withdrawal). Axitinib treatment may be adjusted by dosing interruption with or without dose reduction (Section 5.4.6). Avelumab treatment modification for drug-related toxicities, including irAEs and infusion-related AEs is described in Section 5.4.6. Axitinib intrapatient dose escalation may occur if relevant criteria are met (see Section 5.4.6.1).

Patients in Arm A who stop one of the two study drugs (avelumab or axitinib) for reasons other than confirmed disease progression as assessed by BICR may continue on single-agent treatment with the other drug until disease progression by BICR assessment (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. At the end of study, Arm A patients who are still deriving clinical benefit from study treatment will be provided with an option for continued study treatment (eg, rollover study).

Patients who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression by BICR assessment 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 who develop confirmed radiological disease progression by BICR assessment on study treatment but are otherwise continuing to derive clinical benefit from study treatment (see Section 5.4.4) will be eligible to continue with avelumab combined with axitinib, or single-agent avelumab, or single-agent axitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

In Arm B, patients will receive:

- Sunitinib PO 50 mg QD on a schedule of 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2 in 6-week cycles).

Treatment with sunitinib may continue until confirmed disease progression assessed by BICR (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD), patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Study Withdrawal).

Patients who develop radiological disease progression assessed by BICR on sunitinib treatment but are otherwise continuing to derive clinical benefit (see Section 5.4.4) will be eligible to continue with sunitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable.

Sunitinib treatment may be adjusted by dosing interruption with or without dose reduction (see Section 5.4.6).

After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression (see Section 7.7).

3.1.2. Tumor Assessments

Anti-tumor activity will be assessed by radiological tumor assessments and will be based on RECIST guidelines v. 1.1[34] for primary and secondary endpoints. [redacted] Computerized tomography (CT) or magnetic resonance imaging (MRI) will include chest, abdomen and pelvis (CAP) at all time points. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Premedication prior contrast media administration as per local guidelines is allowed (see Section 5.8.5). Bone scintigraphy/bone scans and brain scans/head CT/MRI are also required at screening. Bone lesion(s) identified at screening by bone scan can be further assessed by CT or MRI as per local practice and subsequently re-assessed by CT or MRI as per tumor assessment schedule. If bone scintigraphy/bone scan is the preferred assessment method for bone lesion(s) as per local practice, re-assessment during study should occur every 12 weeks after randomization. Bone scan will also be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of complete response (CR) confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at screening, otherwise brain will only be evaluated when clinically indicated.

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

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, at 6 weeks from randomization, then every 6 weeks up to 18 months after randomization and every 12 weeks thereafter until documented confirmed disease progression by BICR assessment (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD) regardless of initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

The schedule of assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point.

CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD. Further details are provided in Section 5.4.4.

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.

[redacted]

Blinded Independent Central Review (BICR) will review all radiological images. All radiographic images will be collected and objectively verified by an independent third-party core imaging laboratory as described in the Study Manual. After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression (see Section 7.7). After review of images by BICR is stopped, confirmation of disease progression ≥4 weeks after the PD was first noticed will no longer be required.

Post IA3, during treatment, tumor assessments will be conducted every 6 weeks from randomization up to 18 months after randomization and every 12 weeks thereafter until disease progression by investigator assessment or initiation of subsequent anti-cancer therapy, whichever is earlier (see Section 5.4.4 for details on treatment continuation after initial evidence of PD).

irRECIST-defined antitumor activity will no longer be collected as per PACL dated 02 September 2019.

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

[redacted]

[redacted]

3.1.3. Safety Assessments

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. However, after the first 9 months of treatment for each patient, the Sponsor in conjunction with E-DMC might consider to reduce the assessment frequency (eg, once every 1 cycle) according to the emerging safety profile of the avelumab plus axitinib combination.

3.1.4. Patient Outcomes

PROs will be assessed using 2 published and validated instruments: FACT-Kidney Symptom Index (FKSI)-19 and EUROQol 5-Dimension (EQ-5D).

3.1.5. Pharmacokinetic/Immunogenicity Assessments

Sparse plasma/serum PK/Immunogenicity sampling will be collected for axitinib, avelumab, and anti-drug antibodies (ADA). Sampling will only be done in patients randomized to Arm A. Refer to the SOA and Section 7.3 for additional details of the PK collections. Samples should be obtained from the opposite arm to the one being used for avelumab IV infusion.

3.1.6. Biomarker Assessments

Mandatory archival and baseline (recent) tumor tissue will be collected from all patients to support investigation and, as appropriate, clinical validation of biomarkers that may predict response to treatment. End of treatment tumor tissue from a *de novo* biopsy may also be obtained unless clinically contraindicated to support investigation of mechanisms of resistance. [redacted] Biomarker assessments are described in the Schedule of Activities and in Sections 7.5 [redacted]

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 or metastatic renal cell carcinoma with a clear cell component. Advanced RCC patients are patients affected by unresectable disease either unresectable locally advanced or metastatic disease;

   - 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 randomization AND 2) the patient has not received any intervening systemic anti-cancer treatment from the time the tissue was obtained and randomization onto the current study. If an FFPE tissue block cannot be provided as per documented regulations then 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,then 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 guideline/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. ECOG PS 0 or 1.

7. No evidence of 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:

   - Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
   - Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
   - Hemoglobin ≥9 g/dL (may have been transfused).

9. Adequate renal function, including:

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

    - Total serum bilirubin ≤1.5 x ULN;
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN.

11. Left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN) as assessed by either multigated acquisition (MUGA) scan or echocardiogram (ECHO).

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

13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception (see Section 4.3.1) 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. The following prior therapies are excluded:

   - Prior systemic therapy directed at advanced or metastatic 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 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 and/or sunitinib as well as any prior therapies with other VEGF pathway inhibitors.

2. Participation in other therapeutic studies within 4 weeks prior to randomization.

3. Patients with newly diagnosed brain metastases or 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 randomization, 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 randomization. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to patient randomization.

5. Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1; however, sensory neuropathy Grade ≤2 is acceptable.

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

   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);

   - Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;

   - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

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 randomization, 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 randomization.

19. Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, LVEF less than LLN, clinically significant pericardial effusion, cerebrovascular accident, transient ischemic attack.

20. Any of the following in the previous 6 months: deep vein thrombosis or symptomatic pulmonary embolism.

21. Evidence of tumor involvement of the myocardium or pericardium or tumor thrombus extending to the heart.

22. Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or prolongation of the QTc interval to >500 msec.

23. 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 randomization (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.

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

25. 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.

26. Pregnant female patients; breastfeeding female patients.

27. 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. Lifestyle 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 or sunitinib monotherapy 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 for patients in Arm A, and for at least 49 days after the last dose of study treatment for patients in Arm B. 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 for patients in Arm A, and for at least 49 days after the last dose of study treatment for patients in Arm B.

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 4.3.1.2);

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 for patients in Arm A, and for at least 49 days after the last dose of study treatment patients in Arm B. 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 Study Manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study 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), axitinib (AG-013736), and sunitinib.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled.

Once the patient has provided a signed Informed Consent Form (ICF) and has met inclusion and exclusion criteria, the Investigator or delegate will request the study treatment assignment using the Interactive Response Technology (IRT) system (interactive web-based response [IWR]/interactive voice response [IVR] system). Study treatment must start within 3 days after patient randomization.

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

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Note: The IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction.

Qualified patients will be randomized in a 1:1 ratio to receive either avelumab in combination with axitinib (Arm A) or sunitinib monotherapy (Arm B).

Allocation of patients will be stratified according to ECOG PS 0 vs 1 and region (United States vs Canada/Western Europe vs the rest of the world). This stratified randomization will be centrally allocated across all centers via the IRT system.

5.2. Patient Compliance

A patient diary will be provided to the patients to aid in axitinib (Arm A) and sunitinib (Arm B) compliance. The diary will be maintained by the patient to include, unchanged, missed or changed axitinib doses (Arm A) or sunitinib doses (Arm B).

In Arm A, patients will be required to return to the investigational site all bottles of axitinib every 6 weeks (at the end of each cycle) during the planned visit at the site. The number of remaining axitinib tablets 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.

In Arm B, patients will be required to return to the investigational site all bottles of sunitinib every 6 weeks (at the end of the cycle) during the planned visit at the site. The number of sunitinib capsules remaining will be documented and recorded at clinic visit. The patient diary may also be used to support this part of the sunitinib accountability process.

The study site must follow up (for example, via a telephone call) with each patient on Cycle 1 Day 5 (±3 days) to confirm that the patient understands and is in compliance with axitinib or sunitinib dosing instructions. If needed, the patient will be re-trained. The same follow-up process will be applied in case the dose of axitinib or sunitinib is modified during the treatment period.

5.3. Investigational Product Supplies

Avelumab (MSB0010718C), axitinib (AG-013736), and sunitinib (SU011248) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed, filed, and the shipment confirmed as directed on the bottom of the Drug Shipment and Proof of Receipt form. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.3.1. Dosage Form(s) and Packaging

5.3.1.1. Avelumab

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20.0 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.

5.3.1.2. 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.

5.3.1.3. Sunitinib

Sunitinib will be supplied as hard gelatin oral capsules containing 12.5-mg or 25-mg equivalents of sunitinib free base in light-resistant HDPE bottles.

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

5.3.2.2. Axitinib

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 IRT system.

Axitinib will be dispensed on Day 1 of each cycle 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.

5.3.2.3. Sunitinib

Sunitinib will be dispensed in opaque plastic bottles to protect the compounds from light. Sunitinib 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.

Sunitinib 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 drug management system.

Sunitinib will be dispensed on Day 1 of each cycle for the arm B 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.

5.4. Administration

All investigational products will be administered on an outpatient basis.

5.4.1. Avelumab

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

Avelumab will be administered on Days 1, 15 and 29 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 dose.

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) to be administered approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acet aminophen] IV or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate. As per Amendment 8, premedication is no longer required unless clinically indicated by the presence/severity of prior infusion reactions. 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 Case Report Form (CRF). Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.4.6.6.

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 infusion. 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 treatment 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 administration may be omitted due to persisting toxicity as described in Table 3 and Section 5.4.6.

Patients experiencing toxicity may require treatment adjustment or discontinuation according to the guidelines specified in Table 3.

5.4.2. 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 5.4.6). 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.

Patients experiencing toxicity may require treatment adjustment or discontinuation according to the guidelines specified in Table 1 and Table 3.

5.4.3. Sunitinib

Sunitinib will be administered orally QD at approximately the same time daily continuously for 4 consecutive weeks followed by a 2-week off-treatment period (Schedule 4/2 in 6-week cycles), Sunitinib capsules are to be taken daily and may be administered without regard to meals. Capsules must not be opened, 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 sunitinib.

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 in the same 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.

Patients experiencing toxicity may require treatment adjustment or discontinuation according to the guidelines specified in Table 2 and Table 4.

5.4.4. Treatment After Initial Evidence of Radiologic Disease Progression in Both Arms

Immunotherapeutic agents such as avelumab may produce anti-tumor 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 as assessed by BICR, tumor assessment should be repeated at least ≥4 weeks later in absence of clinical deterioration in order to confirm disease progression. This confirmation of disease progression assessed by BICR will not affect the primary and secondary endpoints defined according to RECIST v.1.1.

Patients will receive study treatment while waiting for confirmation of PD in absence of clinical deterioration, as defined by the following criteria:

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

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

If the repeat imaging confirms PD by BICR assessment, patients should be discontinued from study treatment. However, according to the investigator's clinical judgment and after discussion between the investigator and the sponsor's medical monitor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with single-agent avelumab, single-agent axitinib, or avelumab in combination with axitinib in Arm A, or sunitinib monotherapy in Arm B (crossover between treatment arms is not permitted). 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.

In patients who continue treatment beyond progression by BICR assessment, the oncologic assessments should continue to be performed as per SoA and be recorded in the CRF until the study treatment is permanently discontinued.

Patients who stop avelumab after initial clinical benefit while on treatment and then experience radiologic disease progression confirmed by BICR 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.

After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression (see Section 7.7). After review of images by BICR is stopped, confirmation of disease progression ≥4 weeks after the PD was first noticed will no longer be required.

5.4.5. Food Requirements

All investigational products may be administered without regard to 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]).

5.4.6. 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 and sunitinib, 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 3. Dose modifications of axitinib and infusion omissions of avelumab may occur independently for the two drugs and will be reported in the CRF.

Available axitinib and sunitinib dose levels for intrapatient dose modification are listed in Table 1 and in Table 2, respectively.

5.4.6.1. Intrapatient Axitinib Dose Escalation and Dose Reduction

Axitinib intrapatient dose increase to 7 and/or 10 mg in combination with avelumab is prohibited in France, as per Agence nationale de sécurité du médicaments et de produits de santé (ANSM) request.

In other countries, intrapatient axitinib dose escalation is permitted up to 10 mg BID and may occur according to the criteria described below.

Patients who tolerate the current axitinib dose without Grade >2 axitinib-related adverse events for 2 consecutive weeks have the option to have their axitinib dose increased (one dose level increase at a time) as indicated in Table 1 (unless the patient's BP is >150/90 mm Hg or the patient is receiving antihypertensive medication). Particular attention should be provided to a patient's overall safety profile prior to implementing intrapatient axitinib dose escalation.

Table 1. Axitinib Dose Levels

Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
Potential 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 3. Dosing interruption and/or dose reduction by 1, and if needed, 2 dose levels (one dose level decrease at a time) as indicated in Table 1 will be allowed depending on the type and severity of toxicity encountered. Management of patients requiring more than 2 dose reductions of axitinib (one dose level decrease at a time) 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.

5.4.6.2. Sunitinib Dose Modifications

Sunitinib dose interruptions and/or dose reduction by 1, and if needed 2 (one dose level decrease at a time), dose level(s) as indicated in Table 2 will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal in Section 6.5 have not been met. If recovery to Grade ≤1 toxicity does not occur within 6 weeks, investigator should discuss with the medical monitor about any dose modification and or treatment continuation. Consult with the medical monitor before discontinuing the patient. No more than 2 dose reductions are permitted in any patient. If more than 2 dose reductions of sunitinib are required, further reductions should be discussed with the sponsor's medical monitor.

Table 2. Sunitinib Dose Levels

Dose Level	Dose
Starting Dose	50 mg QD
-1	37.5 mg QD
-2	25 mg QD

Sunitinib dose re-escalation back to the previous dose level is permitted in the absence of Grade ≥3 hematologic or Grade ≥2 non-hematologic treatment-related toxicity during the previous treatment cycle.

5.4.6.3. Management of Axitinib- or Sunitinib-Related Hypertension

Patients will be issued BP cuffs (provided by the sponsor) for home monitoring and instructed to measure their BP at least once daily (in Arm A before taking the morning dose of axitinib, and in Arm B before taking the daily dose of sunitinib during the 4 weeks of

treatment and any time during the day in the 2 weeks off treatment). 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 therapy and patients should be monitored for hypertension.[38,39] To treat an increase in BP, standard antihypertensives may be used (eg, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and calcium channel blockers, [except diltiazem since it is a strong CYP3A4 inhibitor],etc.).[38,39]

For patients on sunitinib therapy, hypertension should be monitored and treated as needed with standard anti-hypertensive therapy.

Dose modifications for axitinib and sunitinib in case of hypertension are described in Table 3.

Post IA3, BP home monitoring will no longer be required.

5.4.6.4. Axitinib Dose Modifications, Avelumab Infusion Omissions, and Sunitinib Dose Modifications for Treatment-Related Toxicity

In Arm A, recommended axitinib dose modifications and avelumab infusion omissions in case of drug related toxicity are shown in Table 3. The aforementioned guidelines might be further modified at the discretion of the sponsor based on the emerging safety profile of the combination. The investigator can consider consulting with the sponsor's medical monitor in case of persistent toxicity that would lead to dose modification or treatment discontinuation per toxicity treatment guidelines.

In Arm B, recommended sunitinib dose modifications in case of drug-related toxicity are shown in Table 4.

The 4-week sunitinib dosing period may not be extended to compensate for interruptions in sunitinib treatment due to any cause. If recovery to Grade ≤1 toxicity does not occur within 6 weeks, investigator should consider consulting with the medical monitor about any dose modification or treatment discontinuation.

Table 3. 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 (consider consult with the 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 (consider consult with 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.	

Table 3. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

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 5.4.6.3 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 5.4.6.3 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 3. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	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 dosing interruption. • See Section 5.4.6.3 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 5.4.6.3 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 3. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	Treatment Modification
Infusion-related Reaction	Grade 1-4	• Continue at the same dose level.	• See Section 5.4.6.6 and Table 5.
Hypersensitivity reactions	Grade 3-4	• Continue at the same dose level.	• See Section 5.4.6.7 and Table 5.
Tumor lysis syndrome	Grade 1-4	• See Other Non-Hematologic Toxicities and/or Laboratory Abnormalities.	• See Section 5.4.6.8 and Figure 1.
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 5.4.6.9 and Table 6.
Stevens-Johnson syndrome	Grade 3-4	• Permanent discontinuation.	• Permanent discontinuation.
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.

Table 3. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib	Avelumab
		Dose Modification	**Treatment Modification**
	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 (consider 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.
	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 (consider consult with the medical monitor before permanently discontinuing the treatment). **Exceptions are:** Laboratory values that do not have any clinical correlate.

In case of LVEF decline in patients treated with the axitinib plus avelumab combination, Investigators are encouraged to consult with the Sponsor to discuss the management of axitinib therapy independently of any actions implemented for avelumab and the Investigator's causality assessment of the event.

Table 4. Sunitinib Dose Modifications for Investigational Product Related Toxicity

Toxicity	Grade 1/2	Grade 3 or intolerable Grade 2	Grade 4
Non-Hematologic (exceptions: CHF, pancreatitis, necrotizing fasciitis, nephrotic syndrome and thrombotic microangiopathy).***	Continue at the same dose level	Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then resume treatment at the same dose level.* If the toxicity recurs with Grade 3 severity (or intolerable Grade 2) at the discretion of the investigator, reduce the dose by 1 level.	Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.*
Hematologic	Continue at the same dose level	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then resume treatment at the same dose level.** If the toxicity recurs with Grade 3 severity, at the discretion of the investigator, reduce the dose by 1 level.	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then reduce the dose by 1 level and resume treatment.**
Left Ventricular Ejection Fraction Reduction.	Continue at the same dose level	The dose should be interrupted and/or reduced if without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.	The dose should be interrupted and/or reduced if without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

*Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the Investigator. Nausea, vomiting, or diarrhea persist at Grade 3 or 4 despite maximal medical therapy.
**Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption. Complicated neutropenia includes duration of Grade 4 longer than 7 days or concurrent fever or infection.
***If occurs sunitinib should be discontinued.

5.4.6.5. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) to be administered 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. Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. As per Amendment 8, the 2 hours observation post-infusion are no longer required unless clinically indicated. 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, and tumor lysis syndrome are outlined in Sections 5.4.6.6, Section 5.4.6.7 and Section 5.4.6.8, respectively.

Investigators should also monitor patients closely for potential irAEs, which may become manifest at any time after the first dose of treatment. Such events may 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 5.4.6.9.

5.4.6.6. 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 5.

Table 5. Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Avelumab

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any 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 infusion tubing from the patient. Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.
IV=intravenous, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs.	

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

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions:

In the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 5 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that avelumab dose. At the next avelumab dose, the investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication as clinically indicated. Prophylactic steroids are NOT permitted.

5.4.6.7. 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.

If hypersensitivity 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.

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

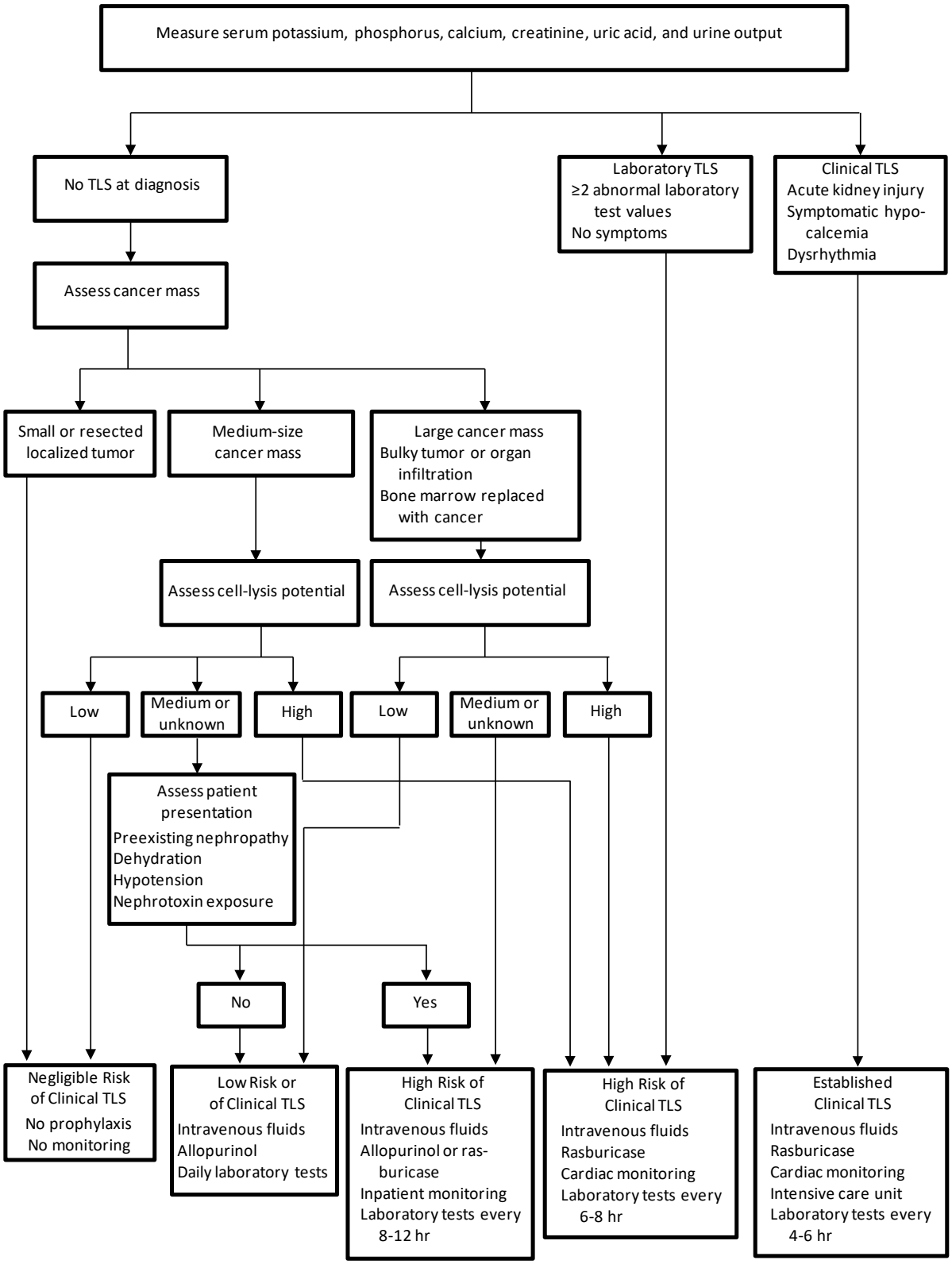
For prophylaxis of flu-like symptoms, 25 mg indomethacin or comparable Nonsteroidal Anti-Inflammatory Drug (NSAID) dose (eg, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered at investigator discretion 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative 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 8 and may be modified based on local treatment standards and guidelines, as appropriate.

5.4.6.8. 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. Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 1) published by Howard et al.[48]

Figure 1. Assessment and Initial Management of Tumor Lysis Syndrome (TLS)



5.4.6.9. 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 as reported in Table 6:

- 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.

For any irAE of any grade, the investigator may consider consulting with the sponsor's medical monitor if deemed necessary.

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

Some potential immune-related adverse events described with anti-PD-L1 monoclonal antibodies such as avelumab may overlap with axitinib toxicities (eg, diarrhea, liver function tests increase). Any adverse event suspected to be immune-related should be managed according to the guidance for management of immune-related adverse events in this Section 5.4.6.9.

For overlapping potential immune-related toxicities Grade 2, hold both drugs used in the combination (avelumab and axitinib) and follow the specific management recommendations described in Table 6. When the event resolves to Grade ≤1, restart therapy with axitinib. If the Grade ≥2 event does not recur, restart avelumab at the next treatment dose. If the Grade ≥2 event does not resolve to Grade ≤1 after holding avelumab for 2 treatment doses (up to 28 days) or if the Grade ≥2 event recurs after re-introduction of avelumab, permanently discontinue avelumab therapy.

For Grade ≥3 overlapping potential immune-related toxicities follow the specific guidance on Table 6 for avelumab and hold axitinib. When event resolved to Grade ≤1, restart therapy with axitinib at reduced dose level. Avelumab should be permanently discontinued.

Table 6. 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 subject 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 stool	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.
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy.	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 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.

Table 6. Management of Avelumab Immune-Related Adverse Events		
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)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy. Monitor for symptoms every 2 to 3 days. Consider Pulmonary and Infectious Disease consults.	Re-assess at least every 3 weeks. If worsens: Treat as Grade 2 or Grade 3 to 4.
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).

Table 6. Management of Avelumab Immune-Related Adverse Events

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. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤1: Taper steroids over at least 1 month. If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
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.

Table 6. Management of Avelumab Immune-Related Adverse Events		
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		

Table 6. Management of Avelumab Immune-Related Adverse Events

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): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL,	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

Table 6. Management of Avelumab Immune-Related Adverse Events

	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.	
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.

Table 6. Management of Avelumab Immune-Related Adverse Events		
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy. 1.0 to 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 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.

5.5. 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. See the dosage and administration instructions (DAI), package insert, or equivalent for storage conditions of the products and once reconstituted and/or diluted (for avelumab only).

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

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

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions 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 available. 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.

5.6. 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 the end of each cycle and at the end of the trial, the sponsor will provide instructions as to disposition of any unused investigational product if the investigative site is unable to destroy at site per local procedures.

5.7. 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.

5.8. Concomitant Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for administration of the inactivated vaccines (for example, 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 in Arm A or sunitinib in Arm B 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 5.4.6.5, Section 5.4.6.6, Section 5.4.6.7, Section 5.4.6.8, and Section 5.4.6.9, respectively.

5.8.1. 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.

Sunitinib is primarily metabolized by liver enzymes, in particular CYP3A4. There was a mean 1.8-fold increase in exposure of sunitinib when co-administered with ketoconazole, a potent inhibitor of CYP3A4 and a mean 4-fold decreased in exposure of sunitinib when co-administered with rifampin, a potent inducer of CYP3A4.

The concomitant use of strong CYP3A4/5 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, diltiazem, telithromycin, and voriconazole) should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although axitinib and sunitinib dose adjustments have not been studied in patients receiving strong CYP3A4/5 inhibitors, consider a dose reduction if axitinib or sunitinib must be dosed with a CYP3A4/5 inhibitor.

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

Coadministration of axitinib or sunitinib 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 or sunitinib and should be avoided if possible. Consider a dose increase if axitinib or sunitinib must be dosed with a CYP3A4/5 inducer.

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

A listing of CYP3A4 inhibitors and inducers will be provided to the sites and updated as needed.

5.8.2. Hematopoietic Growth Factors

Granulocyte colony stimulating factor may be used in agreement with American Society of Clinical Oncology (ASCO) guidelines.[58]

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.

5.8.3. 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's medical monitor.

The appropriate interval of time between surgery and sunitinib treatment required to minimize the risk of impaired wound healing and bleeding has not been determined. Based upon pharmacokinetic and clinical considerations of sunitinib, stopping sunitinib treatment is recommended at least 14 to 21 days prior to major elective surgery and at least 5-7 days before minor surgery. Postoperatively, the decision to reinitiate sunitinib treatment should be based upon a clinical assessment of satisfactory wound healing and recovery from surgery.

5.8.4. Concomitant Radiotherapy

Local radiotherapy (limited field) of isolated lesions with palliative intent is acceptable and allowed throughout the study (ie, starting from screening trough 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 also be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression. Consult the sponsor's medical monitor prior to starting radiotherapy or prior to restarting study treatment after the end of radiotherapy.

5.8.5. Other Prohibited Concomitant Medications and Therapies

Patients enrolled on both arms are prohibited from receiving the following therapies while receiving study treatment:

- 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 inactived vaccines (for example, inactivated 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 study treatment. The need to initiate while on study treatment or increase the dose of these therapies during the study for patients who started >14 days before study treatment start, will be considered as indicative of disease progression leading to the discontinuation of patient from the study treatment unless disease progression can be completely ruled out and the exact reason for the use of these therapies must clearly be documented.

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

- Other experimental pharmaceutical products.

- Herbal remedies with immunomodulating 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.[40,41] 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-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes.[42] 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 6.

- 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.

5.9. Rescue Medications and Supportive Care

5.9.1. 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 6.

- 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 (SOA) and Assessments section (Section 7).

6.1.1. Tumor Biospecimens

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

- **Recent tumor biospecimen**: a mandatory formalin-fixed, paraffin-embedded (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. Alternatively a recent archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue block [redacted] can be provided [redacted]

- **Archival tumor biospecimen**: a mandatory archival FFPE tumor tissue block from the primary diagnosis specimen must be provided from all patients prior to randomization. [redacted]

- End of Treatment Tumor Biopspecimen: A *de novo* tumor sample (ie, fresh biopsy) [redacted]

[redacted]

[redacted]

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 formalin-fixed and paraffin-embedded 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. Treatment Period

For treatment period procedures, see Schedule of Activities (SOA) and Assessments (Section 7). Of Note: From Cycle 2 onward, patients randomized to Arm B (Sunitinib Arm), are allowed to visit the site once per cycle as per clinical standard practice. Patients in Arm A who have permanently discontinued avelumab and continue on treatment with single agent axitinib, will be required to visit the site every 2 weeks for additional 2 full cycles following avelumab discontinuation and then allowed to visit the study site only once per cycle as per standard clinical practice, unless clinically contraindicated. Days 15 and 29 safety data as specified in the Schedule of Activities footnotes will be collected by email/fax and telephone call unless the patient is visiting the site for other reasons. Based on observed (laboratory tests) and reported findings during the call, the patient might be required to visit the site. The Investigator must document in writing the results of the phone call in a specific form and data are to be reported in the CRF.

Post IA3, Days 15 and 29 safety assessments other than pregnancy tests will no longer be required unless clinically indicated. Note: pregnancy test will be required on Days 1 and 29 only.

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

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

All patients will be followed for survival every 3 months (±14 days) until death, end of the study or patient withdrawal of consent, whichever comes first. Information will be collected by telephone unless the patient is visiting the site for other reasons. The investigator or designee must make every effort to collect the patient's status through contacting the patient or a relative or their usual health care provider by telephone or other allowed methods. These contact attempts should be documented in the patient's medical records. See Schedule of Activities (SOA) for further details.

6.4. End of the Study

The study will end when at least 368 OS events in the PD-L1+ population (patient population prospectively defined as noted in Section 7.5.1) have occurred.

At the end of study, Arm A patients who are still deriving clinical benefit from study treatment will be provided with an option for continued study treatment (eg, rollover study).

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 confirmed disease progression assessed by BICR (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD). However, patients with confirmed disease progression assessed by BICR 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, or with sunitinib provided that the treating physician has determined that the benefit/risk for doing so is favorable. After review of images by BICR is stopped following the planned final analyses for PFS specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression.
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity in Arm A is attributed to one of the two study treatments, the investigator (in discussion with the sponsor's medical monitor) 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, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he 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 assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs and physical examination, Electrocardiogram (ECG, 12-lead), laboratory assessments, including pregnancy tests and verification of concomitant medications.

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. Of Note: From Cycle 2 onward, patients randomized to Arm B (sunitinib Arm) are allowed to visit the site once per cycle as per clinical standard practice. Patients in Arm A who have permanently discontinued avelumab and continue on treatment with single agent axitinib, will be required to visit the site every 2 weeks for additional 2 full cycles following avelumab discontinuation and then allowed to visit the study site only once per cycle as per standard clinical practice, unless clinically contraindicated. Days 15 and 29 safety data as specified in the Schedule of Activities footnotes will be collected by email/fax and telephone call unless the patient is visiting the site for other reasons. Based on observed (laboratory tests) and reported findings during the call, the patient might be required to visit the site. The Investigator must document in writing the results of the phone call in a specific form and data are to be reported in the CRF.

However, after the first 9 months of treatment of each patient, the Sponsor in conjunction with E-DMC might consider to reduce the assessment frequency (eg, once every 1 cycle) according to the emerging safety profile of the avelumab in combination with axitinib.

Post IA3, Days 15 and 29 safety assessments other than pregnancy test will no longer be required unless clinically indicated. Note: pregnancy test will be required on Days 1 and 29 only.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study treatment - once at the start of screening, and once at the baseline visit immediately before the administration of avelumab in combination with axitinib or of sunitinib. 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. Serum or urine pregnancy tests will also be routinely repeated on Days 1, 15, and 29 of every cycle (on Days 1 and 29 only post IA3) during the active treatment period, at the end of study treatment, at 30 ±3, 60 ±3 (Arm B only) Days Follow-up 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.

Post IA3, Day 29 pregnacy test result will be collected by telephone call.

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

Hematology, blood chemistry, coagulation and urinalysis will be collected at the time points described in the Schedule of Activities (SOA) and analyzed at local laboratories. They may also be performed when clinically indicated. Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours) and followed up as per standard clinical practice unless differently specified in the study protocol.

The required laboratory tests are listed in Table 7.

Table 7. Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	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*		PTT or aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Total Calcium*			
	Corrected Calcium (at screening only)§			
	Total Bilirubin* °			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Phosphorus or Phosphate*			
	Albumin			
	Total Protein			
	Uric Acid			
	Amylase			
	Gamma glutamyl transferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase			
	Triglycerides			
	HBV, HCV testing			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH			
	Cardiac Enzymes: B-type natriuretic peptide (BNP), troponin, and CK-MB (as per SoA).			

°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 or aPT)/INR, alkaline phosphatase.
§Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4].

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPT=activated prothrombin time, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BNP=B-type natriuretic peptide, BUN=blood urea nitrogen, CK-MB=Creatine kinase-MB, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, TSH=thyroid-stimulating hormone, WBC=white blood cell.

Table 8. Required Laboratory Tests Post IA3 Cut Off Date (28-Apr-2020)

Hematology	Chemistry Panel	Pregnancy Tests
Hemoglobin	ALT	For female patients of childbearing potential, serum or urine
Platelets	AST	
WBC	ALP	
Absolute Neutrophils	Total Bilirubin°	
Absolute Lymphocytes	GGT	
	Amylase	
	Lipase	
	Potassium	
	Sodium	
	Total Calcium	
	Creatinine	
	Creatine kinase	
	Glucose (non-fasted)	
	Cholesterol	
	Triglycerides	
	Thyroid Function Tests: Free T4, TSH	
	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 or aPT)/INR, alkaline phosphatase.

Abbreviations: ACTH=adrenocorticotropic hormone; ALP= alkaline phosphatase; ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=gamma-glutamyl transferase, T4=thyroxine, TSH=thyroid-stimulating hormone, WBC=white blood cell.

7.1.4. Physical Examinations and Vital Signs

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

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

Vital signs (blood pressure, pulse rate) will be measured on study days as described in the Schedule of Activities (SOA). Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes. Two blood pressure/pulse readings will be taken at least 1 hour apart at each clinic visit. In addition, all patients will be monitoring BP at home as described in Section 5.4.6.3.

Post IA3, physical examination in the clinic and BP home monitoring will no longer be required.

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. On-treatment ECGs will be performed as outlined in the SOA table. 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 sample draws for PK, ECG assessment (as well as CK and troponin, if clinically indicated) 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, 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 (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), then 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. At that time, CK and troponin should be performed in association with clinically indicated ECG assessements. When coinciding with blood sample draws for PK, ECG assessment (as well as CK and troponin, if clinically indicated) should be performed prior to PK blood sample collection, such that the PK blood sample is collected at the nominal time.

7.2. Patient-Reported Outcome Assessments

In this trial, PROs will be assessed using 2 published and validated instruments: FACT-Kidney Symptom Index (FKSI)-19 (Appendix 4) and EuroQol 5-Dimension (EQ-5D) (Appendix 5).

7.2.1. FKSI-19

The FKSI-19 was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system. It is an instrument specifically designed to be a stand-alone instrument to measure symptoms and quality of life in patients with advanced kidney cancer. It contains 19 questions, some of which overlap with the FACT-G questions.[43] The FKSI-19 was developed in order to more comprehensively cover the items of interest in the quality of life measurement for aRCC patients. A 9-item subscale of the FKSI known as the FKSI-Disease Related Symptoms subscale (FKSI-DRS) measuring advanced kidney cancer

disease related symptoms was created using inputs from oncologists and patients.[44] This subscale includes the following 9 items: lack of energy, pain, losing weight, bone pain, fatigue, shortness of breath, coughing, bothered by fevers, and hematuria. A parallel analysis from the FKSI validation study has been carried out to confirm the validity of this FKSI-DRS subscale. The FKSI-DRS has been a subscale of both the FSKI-15 and the FSKI-19. In validation studies, a change of 2-3 points has been established as the Minimally Important Difference (MID) for the FKSI-DRS.[45]

The FKSI-19 questionnaire will be administered on the Cycle 1 Day 1, then at the beginning of the each treatment cycle as well as upon End of Treatment/Withdrawal. Beyond End of Treatment (ie, follow-up period), PRO assessments will be collected at the same time a tumor assessment is performed. The amount of time for a patient to complete the FKSI-19 questionnaire is estimated to be about 3-5 minutes.

7.2.2. EuroQoL EQ-5D

The EuroQol EQ-5D is a 5-item patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[46] There are two components to the EQ-5D; a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.[47] Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction.

The EQ-5D questionnaire will be administered on Cycle 1 Day 1, then at the beginning of each treatment cycle, as well as upon End of Treatment/Study Withdrawal. Beyond End of Treatment (ie, follow-up period), PRO assessments will be collected at the same time a tumor assessment is performed. The amount of time for a patient to complete the EQ-5D questionnaire is estimated to be about 2 minutes.

7.3. Pharmacokinetics Assessments (Arm A only)

PK blood samples will be collected from patients in Arm A only.

7.3.1. Blood Sample Collection for Pharmacokinetic Analysis

PK samples will be collected from patients in Arm A only. Blood samples for axitinib PK and avelumab PK will be collected as outlined in SOA table. Where noted in the SOA table, PK blood samples will be collected at approximately the same time as other assessments wherever possible.

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

In addition to PK blood samples collected at the scheduled times, additional PK 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 blood 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 PK blood sample collection cannot be completed for any reason, the missed sample collection may be rescheduled with agreement of the investigator and sponsor.

Patients who discontinue treatment with axitinib or avelumab do not need to continue the collection of the PK samples for the discontinued drug.

PK blood 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.

7.3.2. 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_3 EDTA tube to provide a minimum of 1 mL plasma for axitinib PK analysis.

7.3.3. 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.

7.4. 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.

7.5. 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 blood biomarkers obtained before, during and after treatment will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of

Treatment/Withdrawal visit enable investigation of potential mechanisms of resistance to the drug combination.

7.5.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Tumor biospecimens from archived tissue samples and metastatic lesions (see Section 6.1.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

[redacted]

Tumor biopsies obtained 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 [redacted]

[redacted]

Computerized tomography (CT) or magnetic resonance imaging (MRI) will include chest, abdomen and pelvis (CAP) at all time points. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. Premedication prior contrast media administration as per local guidelines is allowed (see Section 5.8.5). Bone scintigraphy/bone scans and brain scans/head CT/MRI are also required at screening. Bone lesion(s) identified at screening by bone scan can be further assessed by CT or MRI as per local practice and subsequently re-assessed by CT or MRI as per tumor assessment schedule. If bone scintigraphy/bone scan is the preferred assessment method for bone lesion(s) as per local practice, re-assessment during study should occur every 12 weeks after randomization. Bone scan will also be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) or at the time of complete response (CR) confirmation. Brain must be included in subsequent tumor assessments if a patient has brain metastases at screening, otherwise brain will only be evaluated when clinically indicated.

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

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, at 6 weeks from randomization, then every 6 weeks up to 18 months after randomization and every 12 weeks thereafter until documented confirmed disease progression by BICR assessment (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD) regardless of initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

The schedule of assessments should be fixed according to the calendar, regardless of treatment schedule, treatment delays or interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point.

CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD. See Schedule of Activities (SOA) and Section 5.4.4 for treatment after initial evidence of disease progression.

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 v. 1.1[34] (Appendix 2) [redacted]

Blinded Independent Central Review (BICR) will review all radiological images. All radiographic images will be collected and objectively verified by an independent third-party core imaging laboratory as described in the Study Manual.

After review of images by BICR is stopped following the final analyses for PFS performed as specified in the protocol (Section 9.6), permanent discontinuation of treatment will be performed as per investigator-assessed disease progression. After review of images by BICR is stopped, confirmation of disease progression ≥4 weeks after the PD was first noticed will no longer be required.

Post IA3, during treatment, tumor assessments will be conducted every 6 weeks from randomization up to 18 months after randomization and every 12 weeks thereafter until disease progression by investigator assessment or initiation of subsequent anti-cancer therapy, whichever is earlier (see Section 5.4.4 for further details on treatment continuation after initial evidence of PD).

irRECIST-defined antitumor activity will no longer be collected as per PACL dated 02 September 2019.

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

7.8. Expedited Blinded Independent Central Review for Disease Progression

To mitigate the potential for bias in determining disease progression, expedited BICR review will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from screening onwards will be submitted to the BICR for expedited review. See the Study Manual for process details. Every effort should be made to keep the patient on study treatment until the BICR has completed the radiographic image review, unless contraindicated by the investigator.

The expedited BICR review performed for the investigator-assessed disease progression will end in parallel with the end of the BICR review.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 90 calendar days after the last administration of the investigational product. SAEs occurring to patients 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 nonserious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least 1 dose of investigational product 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 investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.3.1. Avelumab Adverse Event 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 5.4.6.9. AESIs are reported according to the general AE reporting rules specified in Sections 8.1 and Section 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 SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

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

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

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

As for axitinib and sunitinib, an overdose is defined as a dose greater than 10 mg BID and 50 mg daily, respectively.

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

For the purpose of this study, an underdose of avelumab, axitinib or sunitinib is defined as the administration of <80% of the planned dose for reasons other than treatment-related toxicities.

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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels 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 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available.

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

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

- Concurrent with:

    - For patients with preexisting 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, 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 a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

- Hospitalization does not include the following:
- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

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

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

Diagnostic and therapeutic 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 sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

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

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

8.10. Exposure During Pregnancy

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

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

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

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

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on 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 (also see Section 6.5 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.

Japan only: After the combination of avelumab with axitinib is approved for the treatment of aRCC by the Japanese Ministry of Health, Labour and Welfare (MHLW), investigators may be requested by Pfizer to obtain specific additional follow-up information if a reported treatment-related non-serious AE is found to be unexpected according to the Japanese Package Insert. If this occurs, the investigator will be required to pursue and provide the additional information to Pfizer; as this information may be more detailed than the information captured on the adverse event case report form. In general, the information will include enough detail regarding the description of the adverse event to allow for a complete medical assessment of the case and independent determination of possible causality. Information regarding other possible causes of the adverse event, such as concomitant medications and illnesses, must also be provided.

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. Sample Size Determination

The primary objective of this study is to demonstrate that avelumab in combination with axitinib is superior to sunitinib in prolonging PFS or OS in previously untreated PD-L1+ patients with aRCC.

Secondary objectives of this study are to demonstrate that avelumab in combination with axitinib is superior to sunitinib in prolonging PFS and in prolonging OS in previously untreated patients with aRCC and that are unselected for PD-L1 expression (referred to as 'all comers' in what follows).

The following statistical hypotheses will be tested to address the primary objective:

H_{01}: $HR_{PFS+} \geq 1$ vs. H_{11}: $HR_{PFS+} < 1$

H_{02}: $HR_{OS+} \geq 1$ vs. H_{12}: $HR_{OS+} < 1$

where HR_{PFS+} and HR_{OS+} are the hazard ratios (*Arm A vs. Arm B)* of PFS and OS, respectively, in the PD-L1+ population.

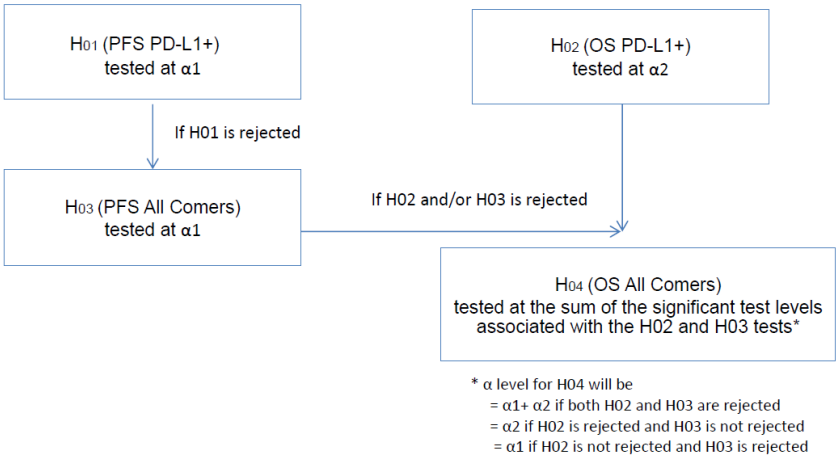
In addition the following statistical hypotheses will be tested to address the secondary objectives:

H_{03}: $HR_{PFS} \geq 1$ vs. H_{13}: $HR_{PFS} < 1$

H_{04}: $HR_{OS} \geq 1$ vs. H_{14}: $HR_{OS} < 1$

where HR_{PFS} and HR_{OS} are the hazard ratios (*Arm A vs. Arm B)* of PFS and OS, respectively, in the 'all comers' population.Overall type I-error will be maintained at or below 1-sided 0.025 by allocating α=0.004 to the PFS comparison in PD-L1+ patients and by allocating α=0.021 to the OS comparison in the PD-L1+ population. A gatekeeping procedure will be used to allow further testing of PFS and OS in the PD-L1 'all comers' population as described in Figure 2. The significance levels for each test will also take into account the group sequential nature of the design (see Section 9.6).

Figure 2. Testing Strategy



For the primary PFS comparison, 336 PFS events by BICR assessment in the PD-L1+ population will provide 90% power to detect a HR of 0.65 using a 1-sided log rank test at a significance level of 0.004, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-15) β-spending function to determine the non-binding futility boundary.

For the primary OS comparison, 368 OS events in the PD-L1+ population will provide 90% power to detect a hazard ratio of 0.70 using a 1-sided log-rank test at a significance level of 0.021, and a 4-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-3) β-spending function to determine the non-binding futility boundary.

The study will randomize a total of approximately 830 patients, including a minimum 580 PD-L1 positive patients, using a 1:1 randomization, stratified by ECOG PS (0 versus 1) and region (United States vs Canada/Western Europe vs the rest of the world).

1. The sample size for this study is determined based on the following: the median PFS for patients receiving sunitinib is 11 months[27] and the median PFS for patients receiving avelumab in combination with axitinib is 16.9 months for PD-L1 positive patients and 15.7 months for patients unselected for PD-L1 expression; this corresponds to a hazard ratio (HR) of 0.65 and 0.7, respectively under the exponential model assumption.

2. The median OS for patients receiving sunitinib is 26.4 months[27] and the median OS for patients receiving avelumab in combination with axitinib is 37.7 months for PD-L1 positive patients and 35.2 months for patients unselected for PD-L1 expression; this corresponds to a hazard ratio (HR) of 0.7 and 0.75, respectively under the exponential model assumption;

3. PFS drop-out rate of approximately 15% and OS drop-out rate of approximately 5%;

4. 70% of the randomized patients are PD-L1 positive;

5. non-uniform patient accrual accomplished over a 21 month period.

The sample size of approximately 830 patients will also allow an assessment of PFS and OS in the 'all comers' population.

If H_{01} is rejected then PFS in the 'all comers' population can be tested and 490 PFS event by BICR assessment will provide 90% power to detect a HR of 0.70 using a 1-sided log rank test at a significance level of 0.004, and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.

If either H_{02} or H_{03} are rejected, then OS in the 'all comers' population can be tested at the sum of the significance levels associated with the significant H_{02} and H_{03} tests (see Figure 2). With 534 OS events, the power is 91% (if both H_{02} and H_{03} are rejected), 90% (if H_{02} is rejected and H_{03} is not rejected) or 74% (if H_{02} is not rejected and H_{03} is rejected) to detect a HR of 0.75 using a 1-sided log rank test at a significance level of 0.025, 0.021 or 0.004, respectively, and a 4-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.

The data cutoff for the primary PFS analysis will occur after the target number of PFS events by BICR assessment in the PD-L1+ population has been reached and the last patient randomized in the study has been followed for at least 12 months after randomization.

The data cutoff for the primary OS analysis will occur after the target number of deaths in the PD-L1+ population has been reached.

The study will be considered positive if the stratified log-rank test for either PFS or OS in the PD-L1+ population is significant at the respective α levels.

9.2. Analysis Populations

For some endpoints, analyses will also be performed on the subset of PD-L1+ patients. The associated analyses sets will be a subset of the analysis sets defined below restricted to the PD-L1+ population.

9.2.1. Full Analysis Set

The full analysis set will include all patients who are randomized. Patients will be classified according to the treatment and stratum assigned at randomization. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Per Protocol Analysis Set

The Per Protocol Analysis Set is a subset of the Full Analysis Set and will include patients who receive at least 1 dose of study treatment (avelumab in combination with axitinib or sunitinib) and do not have major protocol deviations expected to impact the primary objective of the study. Major protocol deviations will be pre-specified in the SAP. The Per-Protocol Analysis Set will be used for sensitivity analyses for the primary efficacy endpoints.

9.2.3. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug (avelumab, axitinib or sunitinib). Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

9.2.4. Pharmacokinetic Analysis Set

The PK concentration analysis set will include all treated patients who have at least 1 concentration above the below limit of quantitation (BLQ) of either of the study drugs in Arm A only.

The PK parameter analysis set will include all treated patients who have at least 1 of the PK parameters of interest of either of the study drugs in Arm A only.

9.2.5. Biomarker Analysis Set

The biomarker analysis set will include all patients who have received at least one dose of the study treatment and who have at least one baseline biomarker assessment.

9.2.6. Immunogenicity Analysis Set

The immunogenicity analysis set will include all treated patients in the avelumab in combination with axitinib arm only, who have at least 1 ADA sample collected.

9.3. Efficacy Analysis

All efficacy analyses will be performed on the Full Analysis Set unless otherwise specified. All analyses will be performed by using SAS® Version 9.1.3 or higher.

All primary and secondary endpoints based on radiological assessments of tumor burden (ie, PFS, OR, DR, DC, TTR) will be derived using the local radiologist's/investigator's assessment. Radiographic images and clinical information collected on-study will also be reviewed by a BICR to verify investigator reported tumor assessments; this information will be used for the primary analysis.

The primary analyses will be repeated on the per-protocol analysis set as a sensitivity analysis. Further details and other sensitivity analyses will be described in the SAP.

9.3.1. Analysis of Primary Endpoints

PFS by BICR assessment in the PD-L1+ population.

In what follows, progressive disease (PD) is based on BICR assessment.

PFS is defined as the time from randomization 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 an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{01}.

PFS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding CI. In order to account for the

group sequential design in this study, the repeated CI (RCI) method,[67] will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of PFS. In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for PFS.

OS in the PD-L1+ population

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

A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{02}. OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding CI. In order to account for the group sequential design in this study, the RCI method,[67] will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of OS. In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for OS.

9.3.2. Analysis of Secondary Endpoints

OS in the 'all comers' population

The methodology described in Section 9.3.1 for OS in the PD-L1+ population will be followed for the assessment of OS in the 'all comers' population. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{04}.

PFS by BICR assessment in the 'all comers' population

The methodology described in Section 9.3.1 for PFS by BICR assessment in the PD-L1+ population will be followed for PFS by BICR assessment in the 'all comers' population. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{03}.

The analyses of PFS outlined based on BICR assessment will be repeated based on the Investigator's assessment. No adjustement for multiplicity will be performed for these secondary analyses based on Investigator assessment.

The analyses of other tumor-related endpoints will be based on the investigator's assessment, as well as on the review of the BICR.

Objective Response (OR)

Objective response is defined as a complete response (CR) or partial response (PR) according to (RECIST v.1.1; Appendix 2) recorded from randomization until disease progression assessed by BICR or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as a non-responder in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) on each randomized treatment arm will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided by treatment arm.

In addition, the best overall response for each patient will be summarized by treatment arm.

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD) according to the RECIST v.1.1 (Appendix 2) recorded from randomization until disease progression assessed by BICR or death due to any cause. DC at 24 weeks is defined as CR, PR or SD ≥24 weeks after randomization and prior to disease progression assessed by BICR or death due to any cause.

The DC rate (DCR) and DCR at 24 weeks on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD overall or ≥24 weeks by the number of patients randomized to the treatment arm. The corresponding exact 2-sided 95% CIs for DCR and DCR at 24 weeks will be provided by treatment arm.

Time to Tumor Response (TTR)

Time to tumor response (TTR) is defined, for patients with an objective response per RECIST v1.1 (Appendix 2), as the time from randomization to first documentation of objective tumor response (CR or PR).

TTR will be summarized by treatment arm using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Duration of Response (DR)

Duration of response (DR) is defined, for patients with an objective response per RECIST v. 1.1 (Appendix 2), as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression assessed by

BICR or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS.

DR will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median DR and 95% CI for the median will be provided for each treatment arm.

PFS on next-line therapy (PFS2)

PFS2 is defined as the time from randomization to discontinuation of next-line treatment, second objective disease progression, or death from any cause, whichever occurs first. PFS2 will be summarized by treatment arm using Kaplan-Meier methodology and displayed graphically, where appropriate. The median PFS2 and 95% CI for the median will be provided for each treatment arm.

Patient-Reported Outcomes (PRO)

The FKSI and EuroQol 5-Dimension (EQ-5D) will be scored according to their respective validation papers and user's guides.

For the FKSI-19, in addition to assessing median change over time between the two treatment groups, a time to deterioration analysis is planned, for the FKSI-DRS. A 3 point change (within group) and a 2 point difference (between groups) has been established as clinically meaningful for this 9-item subscale. Time to 3 point deterioration of FKSI-DRS will be analyzed by a log-rank test stratified by randomization stratification factors. The time to deterioration associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25^{th}, 50^{th} and 75^{th} percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI. The EuroQoL EQ-5D consists of 2 parts, the EQ-5D index (or simply EQ-5D) and EQ-VAS. The EQ-5D comprises 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). A unique EQ-5D health state is defined by combining one level from each of the 5 dimensions and is converted to a single summary index or health utility value. The EQ-VAS is a visual analog scale where the patient indicates how good or bad his health is today by marking an appropriate point on a line between 0 to 100, which correspond to the worst and best imaginable health states.

Missing values in the PRO instruments FKSI and EQ-5D will be handled following the guidance from their respective User Manuals. For the FKSI multi-item scales, the score may be imputed as the mean of the non-missing questions if at least half the questions in that scale are answered. For EQ-5D, the entire score for that cycle is deemed missing if the answer to any one of the 5 dimensions is missing. EQ-5D will be analyzed by using repeated measures model.

Pharmacokinetic Analysis of Avelumab and Axitinib (Arm A Only)

Standard plasma PK parameters for axitinib will be estimated using non-compartmental analysis. For axitinib, standard PK parameters will include C_{max} and C_{trough}. Descriptive statistics for the PK parameters for axitinib will be provided by dose, cycle and day of assessment in tabular form.

Axitinib C_{trough} and C_{max} 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, and day. The trough concentrations for axitinib will be plotted for each dose using a box-whisker plot by cycle and day in order to assess the attainment of steady state.

Avelumab C_{trough} 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, 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.

The central laboratory, analytical laboratory, and Pfizer clinical assay group colleagues will be unblinded; avelumab and axitinib PK samples collected from Arm A (investigational arm) will be sent to the analytical lab for analysis. If the need arises for an early analysis of the PK data (before database lock and release of the randomization codes for the study), a PK unblinding plan will be developed. A PK analyst, who is not associated with the study team, will conduct the analysis to avoid unblinding of the study team.

Immunogenicity Assessment (Arm A Only)

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies each will be reported. 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.

Population Pharmacokinetic and Exposure Response Analysis

Avelumab disposition will be evaluated using a population PK model for the drug and the relationship between exposure and efficacy and safety endpoints will be explored, as necessary, based on emerging efficacy and safety data. The results of these modeling analyses may be reported separately from the clinical study report.

Analysis of Biomarker Endpoints

Biomarker status (ie, positive or negative) may be determined by a predictive biomarker test with an established scoring algorithm defining positive and negative that is developed by the Sponsor. Analysis of primary and secondary efficacy endpoints in sub-groups defined by biomarker status will be performed and reported as described above. Comparisons will be made between biomarker sub-groups (positive and negative) within treatment arms and between treatment arms within biomarker sub-groups.

9.4. Analysis of Other Endpoints

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

9.4.1. Statistical Analysis of Biomarker Endpoints

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

[redacted]

9.5. Safety Analysis

The Safety Analysis Set will be the primary population for safety evaluation. Summaries of AEs and other safety parameters will be provided, by treatment arm, as appropriate.

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 Grade. Adverse events 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 or higher, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for AEs of clinical interest may be further assessed as described in the SAP.

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.

Time to treatment discontinuation/failure due to toxicity

Time to treatment discontinuation/failure due to toxicity is defined as the time from first dose of study treatment to discontinuation of study treatment due to an adverse event or death due to study treatment toxicity. Time to treatment discontinuation/failure due to toxicity will be summarized by treatment arm using Kaplan-Meier methodology and displayed graphically, where appropriate. The median time to treatment discontinuation/failure due to toxicity and 95% CI for the median will be provided for each treatment arm.

Treatment discontinuation due to toxicity

Treatment discontinuation due to toxicity is defined as the discontinuation of study treatment due to an adverse event or death due to study treatment toxicity. The rate of treatment discontinuation due to toxicity in each treatment arm will be estimated by dividing the number of patients who meet the above criteria by the number of patients in the safety set. The corresponding exact 2-sided 95% CIs will be provided for each treatment arm.

Laboratory Abnormalities

The laboratory 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.

MUGA or ECHO

Reports and assessments of cardiac function will be recorded. MUGA or ECHO scan results will be summarized using NCI CTCAE version 4.03 by treatment group.

Electrocardiograms

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

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

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

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

9.6. Interim Analysis

The interim and the primary analyses for each endpoint will be performed based on the Full Analysis Set after all patients have been randomized in the study and the target number of events has occurred as described below. A maximum of 4 distinct analyses cutoffs are planned in the study:

- at the time when approximately 235 PFS events (70% of the expected 336 events) by BICR assessment have occurred in the PD-L1+ population (IA for PFS and IA1 for OS);
- at the time when 336 PFS events by BICR assessment have occurred in the PD-L1+ population (primary analysis for PFS and IA2 for OS);
- 15 months after the primary analysis for PFS (IA3 for OS);
- at the time when 368 deaths have occurred in the PD-L1+ population (primary analysis for OS).

Table 9 displays the maximum number of analyses expected for each of the primary endpoints and the associated efficacy and futility boundaries. The futility boundaries are non-binding but the study may be stopped for futility if at the time of the first interim analysis, both PFS and OS in the PD-L1+ population cross the corresponding futility boundaries. If the efficacy boundary is crossed, for either of the primary endpoints, at the time of an interim analysis or at the time of the primary analysis then the primary objective of the study will have been demonstrated.

Table 9. PFS and OS in the PD-L1+ population – Efficacy and Futility Boundaries

Endpoint	**PFS in PD-L1+**		**OS in PD-L1 +**			
Analysis	**IA1**	**PA**	**IA1**	**IA2**	**IA3**	**PA**
Analysis cutoff trigger	*235 PFS events in PD-L1+*	*336 PFS events in PD-L1+*	*235 PFS events in PD-L1+*	*336 PFS events in PD-L1+*	*15 months after IA2*	*368 deaths in PD-L1+*
Number of events (Information fraction)	235 (70%)	336 (100%)	125 (34%)	195 (53%)	294 (80%)	368 (100%)
p-value (z-value) for efficacy	<0.0006 (<-3.2493)	<0.0038 (<-2.6682)	<0.00007 (<-3.7913)	<0.0015 (<-2.9686)	<0.0093 (<-2.3524)	<0.0180 (<-2.0975)
p-value (z-value) for futility [a]	>0.4059 (>-0.2380)	NA	>0.6411 (>0.3614)	>0.3672 (>-0.3394)	>0.0879 (>-1.3537)	NA

[a] Non-binding.
IA1 = interim analysis 1, IA2 = interim analysis 2, IA3 = interim analysis 3, PA = primary analysis
The observed number of events at the IAs may not match the planned number of events. The efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions.

Table 10 displays the analyses triggers for PFS and OS in the 'all comers' population, as well as the associated efficacy boundaries. As described in Section 9.1, the significance level for the analyses of these endpoints is determined by the closed testing procedure.

Table 10. PFS and OS in the 'All Comers' Population – Efficacy Boundaries

Endpoint	**PFS in 'All Comers'**		**OS in 'All Comers'**			
Analysis	**IA1**	**PA**	**IA1**	**IA2**	**IA3**	**PA**
Analysis cutoff trigger	*235 PFS events in PD-L1+*	*336 PFS events in PD-L1+*	*235 PFS events in PD-L1+*	*336 PFS events in PD-L1+*	*15 months after IA2*	*368 deaths in PD-L1+*
Number of events [a] (Information fraction)	343 (70%)	490 (100%)	182 (34%)	283 (53%)	427 (80%)	534 (100%)
p-value (z-value) for efficacy [b]	<0.0006 (<-3.2478)	<0.0038 (<-2.6683)	<0.00012 (<-3.6656)	<0.0020 (<-2.8726)	<0.0115 (<-2.2727)	<0.0212 (<-2.0286)

[a] Number of events expected under H_{13} for PFS (assuming a HR of 0.7) and H_{14} for OS (assuming a HR of 0.75).
[b] The p-values and z-values noted for OS are those associated with the scenario when both H_{02} and H_{03} are rejected.
IA1 = interim analysis 1, IA2 = interim analysis 2, IA3 = interim analysis 3, PA = primary analysis
The observed number of events at the IAs may not match the planned number of events. The efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-spending functions.

[redacted] The efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions. Therefore, the observed Z-test statistic at the interim analysis will be compared with the updated efficacy and futility boundaries. If the study continues to final analysis, the p-value that will be used to declare statistical significance at the final analysis for each endpoint will be based on the actual number of events documented at the cut-off date for the final analysis and the α already spent at the interim analysis. Further details will be provided in the Statistical Analysis Plan.

If the results of the interim analysis indicate serious safety concerns, the sponsor, in conjunction with an external Data Monitoring Committee (E-DMC), will communicate with the Health Authorities regarding stopping the clinical trial.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety and efficacy of patients in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The E-DMC will perform a preliminary review of safety data, without holding of recruitment, for the first 30 patients randomized in a 1:1 ratio and treated in the study, who have been followed for at least 6 weeks each after the first dose. The E-DMC assessment will be conducted based on the available safety data of the first 30 patients and on all the available safety data of other patients treated up to the data cut-off. Subsequently, the E-DMC will convene to monitor safety in the study approximately every 6 months after the first meeting.

Recommendations for study conduct (continue as planned, continue with modifications, terminate) including whether the study has met the pre-specified minimal futility or efficacy criteria will be conveyed to the sponsor by the E-DMC chair.

9.8. Cardiac Events Adjudication Committee

An independent cardiac events adjudication committee will be established to review selected cardiac adverse events reported in the study in order to confirm the diagnosis and relationship to study treatment, as described in the relevant charter. AEs that will be selected and any other relevant data for this review will be pre-specified in the cardiac events adjudication charter and endorsed by the committee.

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.

Japan only: After the combination of avelumab with axitinib is approved for treatment of aRCC by MHLW, this study will be conducted according to Good Post Marketing Surveillance Practices (GPSP) in addition to GCP.

These changes are regulatory requirements only applied to Japan. As per Japan regulation, once the investigational drug is approved by MHLW in Japan, the clinical trial should be conducted as a post-marketing clinical study. Consequently, upon approval of the combination of avelumab with axitinib in Japan, references to Study B9991003 using the terms “clinical study” or “clinical trial” mentioned in the protocol will be interpreted as “post-marketing clinical study”.

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, from the IRB/EC (in addition to the national completent authority). Changes introduced to a clinical trial related documents, if classified as substantial, must also be approved by the IRB/EC (in addition to the national competent authority) before it can be implemented. 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 2013). The Declaration of Helsinki 2013 will be complied with by the following provision: " At the end of the study, Arm A patients who are still deriving clinical benefit from study treatment will be provided with an option for continued study treatment (eg, rollover study)" as described in Sections 3.1.1 and Section 6.4.

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 Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab 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.[34]

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 randomization 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 the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate “too small to measure and judged to be less than 10 mm” and 5 mm will be used in the calculation of the sum of the diameters.

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 (ie, Not Evaluable), 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 and the Sponsor 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. 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, (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), 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.

- Not Evaluable 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 (if being followed). 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 (if being followed).

- 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.

- Not Evaluable Progression has not been determined and

  - one or more non-target sites were not assessed or

  - assessment methods used were inconsistent with those used at baseline or

  - one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images) or

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

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.

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.

Determination of Tumor Response by RECIST

When both target and non-target lesions are present, individual assessments will be recorded separately. New lesions will also be recorded separately. Determination of tumor response at each assessment based on target, non-target and new lesions is summarized in Table 11.

Table 11. Objective Response Status at Each Assessment for Patients with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD r not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

*Non-PD includes CR and Non-CR/Non-PD
**New lesions must be unequivocal

Determination of Best Overall Response

The best overall response is the best response recorded from randomization until disease progression (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 randomization at a minimum interval of 6 weeks.

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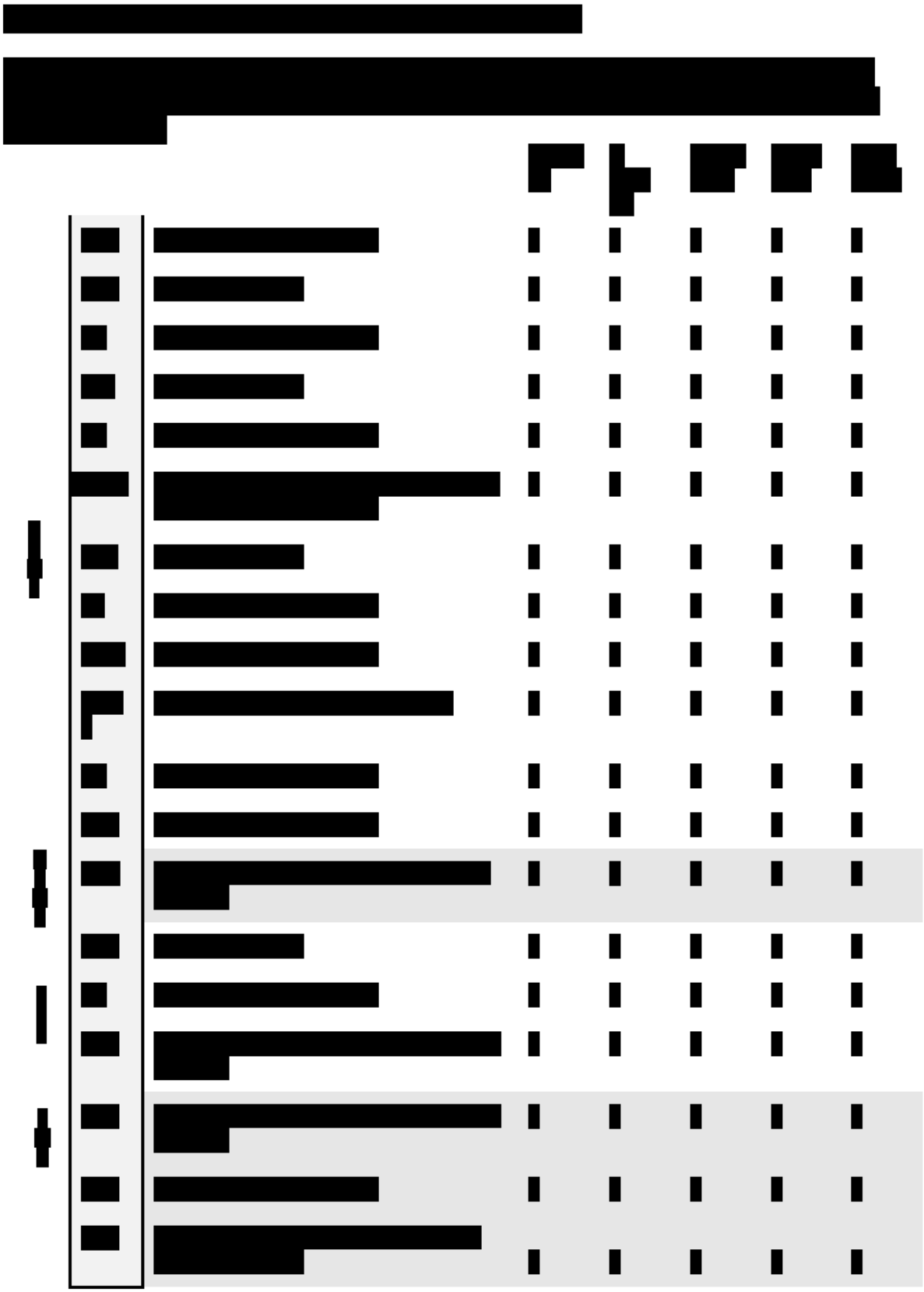

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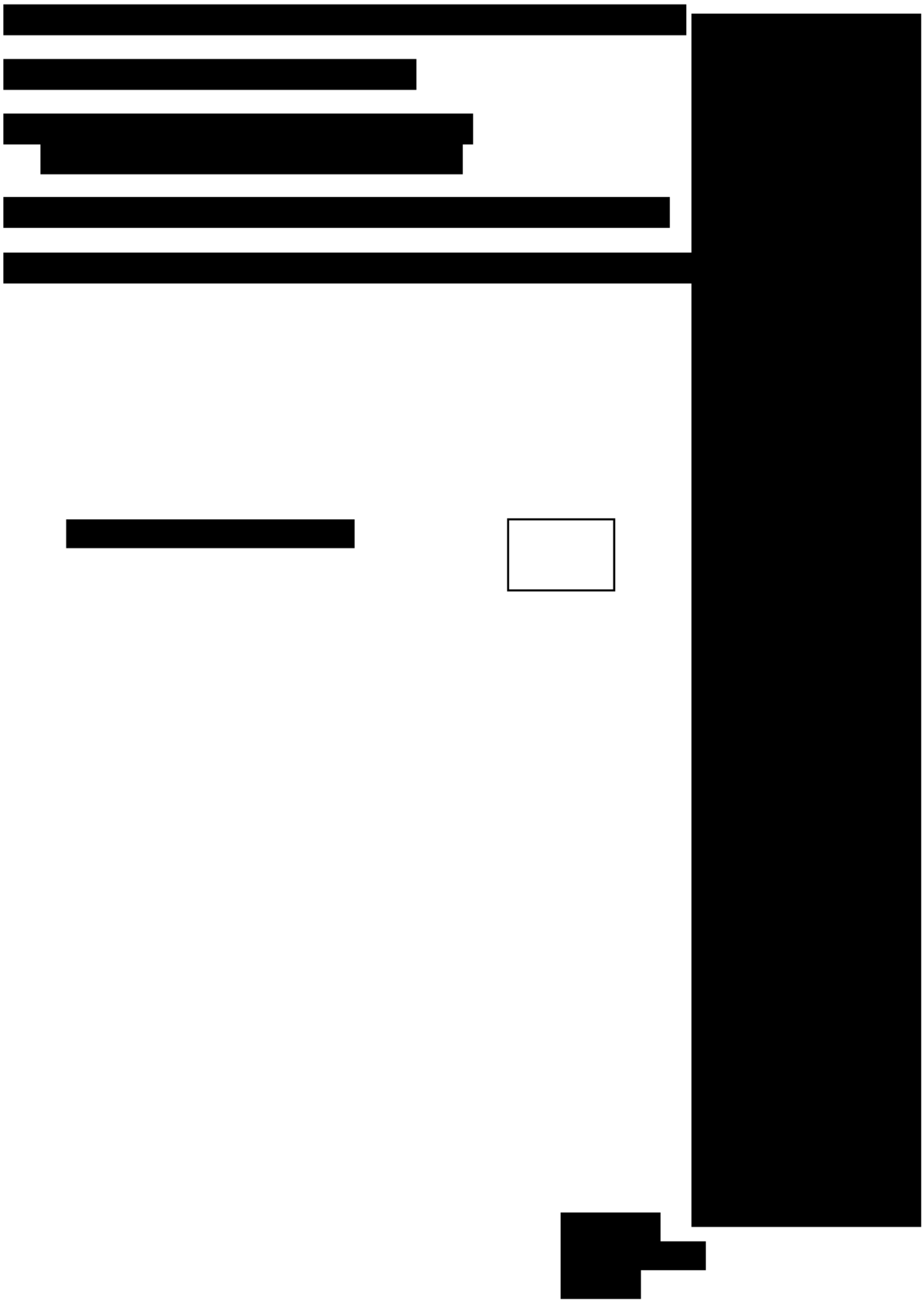

Appendix 6. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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 7. Abbreviations and Definitions of Terms

Ths is a list of abbreviations that may be used in the protocol

ACTH	Adrenocorticotropic hormone
ADA	Anti-Drug Antibody
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
ANSM	Agence nationale de sécurité du médicaments et de produits de santé
aRCC	Advanced Renal Cell Cancer
ASCO	American Society of Clinical Oncology
ASHP	American Society of Hospital Pharmacists
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
BID	Twice Daily
BNP	B-type natriuretic peptide
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAP	Chest, Abdomen, Pelvis
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Plasma Concentration
Cmin	Minimum Plasma Concentration
CK	Creatinine Kinase
CK-MB	Creatine Kinase isoenzyme MB
CR	Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events (US NCI)
CYP1A2	Cytochrome P450 enzyme-1A2
CYP3A4/5	Cytochrome P450 enzyme-3A4/5
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
E-DMC	External Data Monitoring Committee

ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Chronic Illness Therapy
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
GPSP	Good Post Marketing Surveillance Practice
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High Density Polyethylene
HIF	Hypoxia-Inducible Factor
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IA	Interim Analysis
IB	Investigator's Brochure
ICH	International Committee Harmonization
IFN	Interferon
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor and Welfare
mRCC	metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
mTOR	Mammalian Target Of Rapamycin
MUGA	Multigated Acquisition
Nab	Neutralizing Antibodies
NCI	National Cancer Institute
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival

PACL	Protocol Administrative Change Letter
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
PET	Positron emission tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PO	Per Os (by mouth)
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
QD	Every Day
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RSI	Reference Safety Information
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SOA	Schedule of Activities
SRSD	Single Reference Safety Document
t½	Plasma elimination half life
T4	Thyroxine
TIL	Tumor Infiltrating Lymphocytes
TKI	Tyrosine Kinase Inhibitor
Tmax	Time to maximum plasma concentration
TSH	Thyroid Stimulating Hormone
TTR	Time to Tumor Response
ULN	Upper Limit of Normal
US	United States
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
VHL	von Hippel-Lindau

Appendix 8. Treatment Recommendations for Symptoms of Infusion-Related Reactions Caused by Avelumab

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.
- 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):

- Temporarily discontinued 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 once infusion related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any 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 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.
- Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.