AN OPEN LABEL, SINGLE ARM PHASE 1B STUDY OF AVELUMAB PLUS AXITINIB AS FIRST LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

Investigational Product Number:	MSB0010718C, AG-013736
Investigational Product Name:	Avelumab, Axitinib
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Phase:	1b

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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 on the Schedule of Activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifiers[1]	**Screening**	**Study Treatment (1 cycle = 14 days)**			**End of Treatment /Withdrawal**[3]	**Post-Treatment Follow-Up**	
	≤28 Days Prior to Enrollment	**Cycle 1**		**Cycles ≥2**		**Short-Term**[4]	**Long-Term**[4]
		Day 1[2]	**Day 8 (±1 day)**	**Day 1 (±3 days)**		**Day 30, Day 60, Day 90 (±3 days)**	**Every 3 months (±14 days)**
Clinical Assessments							
Informed Consent[5]	X						
Medical/Oncological History[6]	X						
Baseline Signs/Symptoms[7]		X					
Physical Examination[8]	X	X	X	X	X	X	
Contraception Check[9]	X	X		X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Vital Signs[10]	X	X	X	X	X	X	
Home Blood Pressure Monitoring[11]		X					
Laboratory Studies							
Hematology[12]	X	X	X	X	X	X	
Blood Chemistry[13]	X	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X	X	
Thyroid Function Tests[14]	X			X (Cycles 4, 7, 13 then Q12W)	X	X	
ACTH[15]	X			X (Cycle 6, then Q12W`)	X	X	
AFP, PIVKA-II[16]	X			X (Q2W)	X		
HBV, HCV Tests[17]	X			X (Cycle 3, then Q4W)		X	
Serum/Urine Pregnancy Test[18]	X	X		X	X	X	
Urinalysis[19]	X	X		X	X		

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 14 days)			End of Treatment /Withdrawal[3]	Post-Treatment Follow-Up	
		Cycle 1		Cycles ≥2		Short-Term[4]	Long-Term[4]
	≤28 Days Prior to Enrollment	Day 1[2]	Day 8 (±1 day)	Day 1 (±3 days)		Day 30, Day 60, Day 90 (±3 days)	Every 3 months (±14 days)
LVEF by MUGA Scan or Echocardiogram[20]	X			X (Q8W)	X	X (Day 30 only)	
12-Lead ECG[21]	X	X		X (up to Cycle 4)	X		
Disease Assessments							
Tumor Assessments[22]	X	Q8W			X		
Survival[23]							X
Other Clinical Assessments							
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Concomitant Medications/Treatments[26]	X	X	X	X	X	X	
New Anticancer Therapy					X	X	X
Study Treatment[27]							
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Axitinib[28]		X					
Other Samplings							
Pharmacokinetics for axitinib[29]		X		X (Cycles 2, 3)			
Pharmacokinetics for avelumab[30]		X		X (Cycles 2, 3, 4, 6, 8, then every 4 cycles)			
[redacted] CCI		[redacted]		[redacted]	[redacted]		
Mandatory Archival or *de novo* FFPE Tumor Tissue[32]	X				X (optional)		
Anti-Avelumab Antibodies and Neutralizing Antibodies[33]		X		X (Cycles 2, 3, 4, 6, 8, then every 4 cycles)	X	X (Day 30 only)	

ACTH=adrenocorticotropic hormone; AFP=α-fetoprotein; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed and paraffin-embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; LVEF=left ventricular ejection fraction; MUGA=multigated acquisition; PIVKA-II= Protein induced by vitamin K absence or antagonist II; QXW=every X weeks.

Footnotes for Schedule of Activities
1. **Visit Identifiers:** All assessments should be performed prior to the start of study treatment unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers.
2. **Visit window:** -3 days visit window is allowed for all laboratory assessments on Cycle 1 Day 1 except for serum/urine pregnancy test.
3. **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 8 weeks.
4. **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, and new systemic anticancer treatment will also be recorded.
5. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.
6. **Medical/Oncological History:** To include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery, locoregional therapy and radiation therapy.
7. **Baseline Signs/Symptoms:** To be recorded predose for all patients on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to study enrollment.
8. **Physical Examination:** Includes an examination of major body systems and weight (height included at Screening only).
9. **Contraception Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.
10. **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 and pulse rate readings will be taken at least 1 hour apart at each clinic visit.
11. **Home Blood Pressure Monitoring:** All patients will receive home blood pressure monitoring devices and blood pressure will be monitored at home. Patients will monitor their blood pressure at least twice daily (before taking each dose of axitinib) and blood pressure should be recorded in a patient diary. Patients should be instructed to contact the site immediately for guidance if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbances), although a different blood pressure threshold for contacting the site may be used according to the investigator's clinical judgment (see Section 5.4.5.2).
12. **Hematology and Coagulation**: Required tests are listed in Table 5. May also be performed when clinically indicated.
13. **Blood Chemistry:** Full chemistry panel (required tests are listed in Table 5) is required as follows: at Screening, Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, then every 6 weeks thereafter, End of Treatment and Short-Term Follow-up. Core chemistry panel (required tests are listed in Table 5) is required as follows: Cycle 1 Day 8, Cycle 3 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 8 Day 1, then every 2 weeks thereafter. If full and core chemistry panels are scheduled at the same visit, only the full chemistry panel will be performed.
14. **Thyroid Function Tests:** Free T4 and TSH will be performed at Screening, Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 13, Day 1, then Q12W thereafter and End of Treatment and at each visit during Short-Term Follow-up. Additional tests should be performed when clinically indicated. .See Table 5.
15. **ACTH:** To be performed at Screening, Cycle 6 Day 1, then Q12W thereafter, at End of Treatment and at each visit during Short-Term Follow-up. Additional tests should be performed when clinically indicated. See Table 5.

16. **AFP, PIVKA-II:** To be performed at Screening, Cycle 2 Day 1, then Q2W thereafter, and at End of Treatment. Additional tests should be performed when clinically indicated. See Table 5
17. **HBV, HCV Tests:** The viral status in the patients with chronic infection by HBV or HCV will be monitored at Screening, Cycle 3 Day 1, then Q4W thereafter, End of Treatment and Short-Term Follow-up .
18. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at two occasions prior to starting combination study treatment: once at the start of screening and at the Cycle 1 Day 1 visit immediately before the administration of avelumab in combination with axitinib. Additional pregnancy tests (serum or urine) will also be routinely repeated at every treatment cycle during the active treatment period, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Boards (IRBs)/Ethics Committees (ECs) or if required by local regulations (see Section 7.1.1).
19. **Urinalysis**: Required at Screening, at Cycle 1 Day 1 and then at Day 1 of every cycle and at the End of Treatment. If protein ≥2+ by semiquantitative method (eg, urine dipstick), protein will have to be quantified by 24-hour urine collection or urine protein creatinine (UPC) ratio. To be performed as clinically indicated at other time points. See Table 5.
20. **LVEF by MUGA Scan or Echocardiogram:** For the evaluation of the LVEF, the technique used at screening will also be consistently used for the following assessments throughout the study..
21. **12-Lead Electrocardiogram (ECG):** See Section 7.1.4 for details. ECG measurements will be obtained at Screening, Cycle 1 Day 1, Day 1 of every cycle up to Cycle 4 and End of Treatment. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. At each time point, 3 consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates) before avelumab infusion and at the end of infusion. When coinciding with blood samples draws for PK, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time. If patient experiences a cardiac or neurologic adverse event (AE; eg, syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. Additional triplicate ECGs may be performed as clinically indicated.
22. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scans (required at baseline and when suspected brain metastasis) and bone scans or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET, required at baseline then every 12 weeks only if bone metastases are present at baseline). Otherwise, bone imaging is required only if new bone metastasis are suspected and at the time of confirmation of complete response for patients who have bone metastases. See Section 7.6. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, and every 8 weeks from Cycle 1 Day 1 until confirmed disease progression. If a patient discontinues the study treatment due to a reason other than disease progression, tumor assessments should be conducted until confirmed disease progression or initiation of new anticancer treatment, whichever come first. Assessments will be performed according to calendar days, regardless of treatment delays or interruptions. Further imaging assessments may be performed at any time if clinically indicated (eg, suspected progressive disease [PD], symptomatic deterioration, etc.). Complete response (CR) and partial response (PR) must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[redacted] See Section 7.6 for additional information.

23. **Survival:** All patients will be followed for survival and subsequent anticancer therapies every 3 months (±14 days) until death, end of the study or patient withdrawal of consent, whichever comes first. For patients refusing to go back to the site a telephone contact is acceptable.
24. **Follow-up for Axitinib 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.
25. **Adverse Events:** Adverse events should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03. For adverse events (AEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of study treatment. Serious adverse events (SAEs) occuring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the study drug are to be reported to the sponsor. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.
26. **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).
27. **Enrollment:** Required information**:** site and patient identifiers and demographic information. Study treatment (avelumab in combination with axitinib) should begin within 3 days of registration.
28. **Study Treatment:** Axitinib will be given orally (PO) twice daily (BID) on a continuous schedule. Avelumab will be given as a 1-hour intravenous (IV) infusion every 2 weeks (see Section 5). Patients who develop disease progression on study treatment but who are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with single agent avelumab, axitinib, or avelumab combined with axitinib, provided that the treating physician has determined that the benefit/risk for doing so is favorable.
29. **Pharmacokinetics for axitinib:** PK samples for axitinib (3 mL) will be collected at pre-dose and 2 hours post-dose on Day 1 of Cycle 1, Cycle 2 and Cycle 3. Details are outlined in Section 7.1.5.
30. **Pharmacokinetics for avelumab:** Blood samples (3.5 mL) for avelumab PK will be collected in all patients: pre-dose and at the end of infusion (immediately before the end of avelumab infusion) on Day 1 of Cycle 1, 2, 3 and 4. After that, trough (pre-dose) samples will be collected at cycles 6 and 8 and then every 4 cycles, ie., every 8 weeks thereafter. Pre-dose samples can be taken up to 2 hours prior to the start of avelumab infusion. Details are outlined in Section 7.1.5.
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32. **Mandatory Archival or *de novo* FFPE Tumor Tissue:** CCI [redacted] The biopsy sample(s) should be formalin-fixed and paraffin-embedded and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. CCI [redacted] or *de novo* tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted. See Section 6.1.1 and Section 7.4.1.
33. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (nAb):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Day 1 of Cycle 1, 2, 3, 4, 6, and 8 and then every 4 cycles, ie., every 8 weeks thereafter. 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. ADA sample at 30 day follow up is collected at 30 days after end of treatment of avelumab regardless of continuation of axitinib therapy. See Section 7.3.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Treatment naïve advanced or metastatic hepatocellular carcinoma

1.2. Background and Rationale

1.2.1. Hepatocellular carcinoma

An estimated 782,500 new cases and 745,500 death of liver cancer occurred worldwide during 2012, with the second leading cause of cancer death. [1] The most common histologic type of primary liver cancer, hepatocellular carcinoma (HCC), arise from hepatocytes. Approximately 80%-85% of primary liver cancers are HCC.[2] The majority of patients with HCC have underlying cirrhosis, most commonly associated with hepatitis B or C, but also attributable to other predisposing factors like aflatoxin B-contaminated food, excessive alcohol intake or hypermetabolic disorders (eg, obesity, diabetes, hyperlipidemia, etc.). Geographical differences in incidence reflect variations in the main causal factors.[3] Whereas viral hepatitis appears to be more prevalent in Asia, several other factors, including mainly alcohol consumption and hypermetabolic disorders arise more frequently in Western countries. HCC treatment is conventionally divided into curative versus palliative approaches and is guided by both the stage of disease and the degree of remaining liver function secondary to frequently underlying cirrhosis. Curative treatments such as surgical resection or liver transplantation, percutaneous ethanol injection and radiofrequency ablation induce complete responses in a high proportion of patients, with a 5-year survival of about 40%-50%. However, fewer than 30% of patients are eligible for these procedures. Most of the patients with HCC are suitable for palliative treatment only because of the extent of their tumor, poor hepatic function, or both.[4] Patients with localized unresectable disease are usually treated with some form of local therapy, including chemotherapy targeted through the hepatic artery combined with embolization (TACE), percutaneous ethanol ablation, hepatic artery infusion of chemotherapy, radiofrequency ablation, and cryosurgery.[3,5] There is no approved chemotherapy for systemic treatment of advanced HCC. Doxorubicin is the most widely used agent in patients without significantly altered hepatic function, and is associated with a response rate of about 15%, but without improvement in 1-year survival rate (between 30%-50% according to the natural history of the disease) and with a high-risk of increased toxicity in patients with altered hepatic function, and impaired performance status (PS).[6,7,8] More aggressive combinations of chemotherapy have proven equally disappointing. For molecular target agent, only sorafenib is approved for systemic treatment of advanced HCC which has not been treated with prior systemic therapy, based on the results from 2 Phase 3 studies in patients with advanced HCC: one is the study in Caucasian population and the other is the study in Asian population.[9,10] However median overall survival (OS) and time to progression (TTP) with sorafenib are only ~1 year and ~4 months, respectively, with frequent dose reductions or discontinuations due to adverse events.[11,12,13] Therefore, more effective and safe therapeutic options for patients with advanced HCC are needed.

1.2.2. 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 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.[14]

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in Phase 1, 2 and 3 clinical protocols in a variety of cancers, including non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, urothelial cancer, head and neck cancer, and Hodgkin's and non-Hodgkin's Lymphomas, as single agent or in combination with chemotherapy, tyrosine kinase inhibitors, radiotherapy, or other immune modulating agents.

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1.2.3. 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).

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 (Ki = 28 picomolar) against the kinase activity of juxta membrane (JM) domain containing human VEGFR 2 recombinant protein. In additional kinase assays, axitinib showed potent and ATP competitive inhibition of the VEGFRs 1, 2, and 3 and PDGFR-β, but not other closely related family kinases. Receptor binding studies and cell based assays confirmed that axitinib is a potent and selective inhibitor of VEGFRs 1, 2, and 3. Axitinib was shown to have antiangiogenic activity in a number of models including spontaneous pancreatic islet cell tumors of RIP TAG 2 transgenic mice model and demonstrated antitumor efficacy including marked cytoreductive antitumor activity in multiple tumor models implanted in athymic mice.

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.

The most common adverse events reported in patients with advanced HCC who received axitinib single agent in randomized Phase 2 study (n = 133) were diarrhea, hypertension, decreased appetite, fatigue, abdominal pain, palmar-plantar erythrodysaesthesia syndrome, weight decreased, nausea, dysphonia and hypothyroidism.[15] Grade 3 events that occurred most frequently were hypertension, diarrhea and palmar-plantar erythrodysaesthesia syndrome. Overall safety profile in patients with advanced HCC was similar to known safety profile of axitinib single agent.

Following twice daily 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 SRSD, which for this study is the axitinib IB. The reference safety information (RSI) can be found in tabular format in Section 7.8 of the axitinib IB.

1.2.4. Clinical Experience of Combination therapy of avelumab plus 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 (PK) and

pharmacodynamics of avelumab in combination with axitinib in patients with previously untreated advanced RCC. This study also evaluated preliminary antitumor activity as secondary endpoint. 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/recommended Phase 2 dose (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 reaction (IRR), vomiting (7 patients each, 14.9%), 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%), 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.

As of 15 August 2016, 17 SAEs were notified to the sponsor. Fourteen (14) out of the 52 treated patients experienced a total of 23 treatment-emergent SAEs, regardless of causality. A total of 12 treatment-related treatment-emergent SAE were reported for 8 patients, including the following events: dehydration, IRR, venous thrombosis, transaminases increased, pyrexia, neutropenia, lipase increased, amylase increased, palpitation, dyspnea, ALT increased, and myocarditis. The patient with myocarditis died suddenly at home after 19 days of treatment with the combination, and 5 days after the second dose of avelumab. The patient had visited the site 5 days before his death and at that time had no signs or symptoms suggestive of cardiac toxicity, nor remarkable laboratory abnormalities. An autopsy was performed and a myocarditis with heavy lymphocytic infiltration was identified as the cause of death. Tests for viral myocarditis were negative. Myocarditis is an expected adverse drug reaction for avelumab.

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).

Currently, this combination is tested in phase 3 (NCT02684006): A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer (JAVELIN Renal 101).

1.2.5. Rationale for Studying Avelumab in Combination with Axitinib in Patients with Advanced Hepatocellular Carcinoma

HCC is a highly vascular tumor in which vascular recruitment and invasion greatly contribute to pathogenesis. The vascular endothelial growth factor (VEGF) is thought to have an important role in HCC angiogenesis; its expression has been confirmed in this disease[16] and has been associated with poor prognosis.[17] The expression of VEGF receptors has also been investigated in HCC, and the results suggest that an angiogenesis mechanism operates via the VEGFR1 or VEGFR2 pathway.[18,19,20,21]

Two oral multi-kinase inhibitors, sorafenib and regorafenib that block the activity of protein kinase involved angiogenesis showed survival benefit in Phase 3 studies. Results from the Phase 3 trial (SHARP) testing single-agent sorafenib in patients with advanced HCC showed a significant improvement in OS compared to placebo from a median of 7.9 months to 10.7 months (hazard ratio [HR] = 0.69 [95% CI: 0.55 - 0.87, p <0.001]).[9] In addition, Phase 3 trial that tested single-agent sorafenib in advanced HCC in Asian patients also showed a significant improvement in OS from a median of 4.2 months to 6.5 months (HR = 0.68 [95% CI: 0.50 - 0.93, p = 0.014]).[10] Based on the results from these Phase 3 trials, sorafenib has been used for 1st line treatment as a standard of care in patient with advanced HCC. Phase 3 study of regorafenib in patients with sorafenib resistant or refractory HCC showed a significant improvement in OS compared to placebo (HR = 0.63 [95% CI: 0.50 - 0.79, p <0.0001]) with median OS of 10.6 months and 7.8 months, respectively.[24] Recently, lenvatinib, VEGFR tyrosine kinase inhibitor, showed promising efficacy results in single arm Phase 2 study in patients with advanced HCC who did not have prior systemic therapy. In this Phase 2 study, median OS was 18.7 months (95% CI: 12.7 - 25.1) and 17 of 46 patients showed PR per modified Response Evaluation Criteria in Solid Tumors (RECIST)[25] (objective response rate [ORR]: 37%).[26]

Although axitinib did not show statistically significant improvement in OS compared to placebo in Phase 2 study in patients with advanced HCC resistant, refractory or intolerant to sorafenib (HR = 0.907 [95% CI: 0.646 - 1.274], p = 0.287)[15], subgroup analysis in the population excluding patients intolerant to sorafenib from the overall population showed clinically significant improvement in OS with median OS of 12.3 months in axitinib arm (N = 121) and 9.2 months in placebo arm (N = 51) (HR = 0.662 [95% CI: 0.458 - 0.956]) (Pfizer internal data). In addition, Japanese and Korean population (excluding patients intolerant to sorafenib) also showed clinically significant results with median OS of 13.9 months in axitinib arm (N = 46) and 4.6 months in placebo arm (N = 17) (HR = 0.479 [95% CI: 0.250 - 0.918]) (Pfizer internal data). The ORR was numerically higher in axitinib arm vs placebo arm (9.7 vs 2.9%; P=0.091) in the overall population.

$CD8^+$ T-cell infiltration into tumor has been reported to correlate with low recurrence rate after resection of HCC,[27] which suggests an immunotherapeutic approach is potentially effective for HCC. PD-1 is one of CD28 superfamily member coinhibitory receptor of T-cell receptor, which binds to PD-L1 or PD-L2. When PD-1 binds to PD-L1 or PD-L2, T-cell proliferation and cytokine release is inhibited.[28] Using the cytokines from tumor-infiltrating lymphocytes expressed into microenvironment, cancer cells express PD-L1 (and sometimes PD-L2) to evade immune surveillance.[29] PD-1/PD-L1 expression in tumor was significantly

correlated with HCC stage, local recurrence rate and poor prognosis.[30] Recently, immune checkpoint inhibitors such as anti-PD-1 and anti-PD-L1 antibodies have been investigated in various types of solid tumors in clinical trials and shows promising antitumor effects. Nivolumab, a high-affinity, fully human anti-PD-1 mAb, approved for treatment of melanoma, RCC and non-small cell lung cancer, has shown durable tumor response with ORR of 20% (95% CI 15 – 26) in 214 patients including 3 complete responses and median OS has not yet been reached but 9-month OS rate of 74% (95% CI 67 – 79) in Phase 1/2 study in patients with advanced HCC.[31]

VEGF can also exert immunosuppressive effects in tumors by inhibiting maturation of dendritic cells, promoting immune suppressive cell infiltration and enhancing immune checkpoint molecule expression,[28] which suggests potential synergy in anti-VEGF therapy in combination with immune checkpoint blockade. The non-clinical and clinical findings described above support investigating axitinib in combination with avelumab in patients with advanced HCC. In this study, the safety and tolerability of the combination of full dose of axitinib plus avelumab (which have showed tolerable safety profile in studies B9991002 and B9991003 in patients with advanced RCC) and the preliminary antitumor effect with the combination will be evaluated in patients with advanced HCC who have not had prior systemic therapy.

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2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the safety and tolerability of avelumab in combination with axitinib as first line treatment in patients with advanced HCC.	• Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate antitumor effect of avelumab in combination with axitinib as first line treatment in patients with advanced HCC per RECIST v.1.1.	• Time to Progression (TTP), Progression Free Survival (PFS), Objective Response (OR), Disease Control (DC), Time to Tumor Response (TTR) and Duration of Response (DR), per RECIST v.1.1.
• To evaluate the OS of avelumab in combination with axitinib in patients with advanced HCC.	• Overall Survival (OS).
• To evaluate the pharmacokinetics of avelumab and axitinib when administered in combination.	• PK parameters including trough and maximum concentrations (C_{trough}, C_{max}) of avelumab and axitinib.
• To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib.	• 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]).
• To assess the immunogenicity of avelumab when combined with axitinib.	• Anti-drug antibodies (ADAs, neutralizing antibodies [nAbs]) for avelumab when in combination with axitinib.
CCI [redacted]	[redacted]
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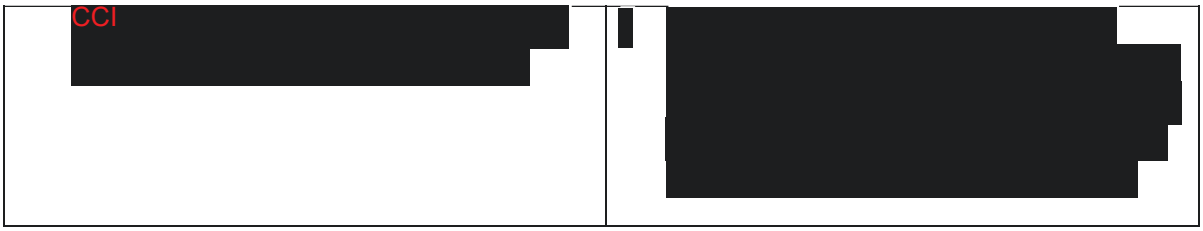

3. STUDY DESIGN

This is an open-label, multi-center, single arm, Phase 1b study to evaluate the safety, efficacy and PK of avelumab in combination with axitinib as first line treatment in patients with advanced HCC.

Approximately 20 patients with advanced HCC who have not had prior systemic therapy will be enrolled in this study. The overall safety profile of these patients will be assessed after a minimum follow up of 3 months (ie. at least 3 months from last patient first dosing [LPFD]). Significant toxicities including irAEs which occur after 3 month follow up will also be included in the assessment.

Patients will receive avelumab 10 mg/kg Q2W in combination with axitinib 5 mg BID. If this dose level for the combination is not tolerable, a lower dose of the combination (avelumab 10 mg/kg IV Q2W plus axitinib 3 mg BID) may be evaluated with adding new cohort of patients. A cohort of patients aimed to evaluate avelumab 800 mg flat dose Q2W in combination with axitinib 5 mg BID may be added after the tolerability of avelumab 10 mg/kg Q2W in combination with axitinib 5 mg BID is confirmed.

Treatment with study drugs may continue until confirmed disease progression, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.3).

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

4. SUBJECT ELIGIBILITY CRITERIA

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 nonmedical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

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

4.1. Inclusion Criteria

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

1. Diagnosis of locally advanced or metastatic HCC, obtained by histology/cytology (on a prior tumor biopsy) or by imaging (acceptable imaging modalities include triphasic contrast-enhanced helical computerized tomography [CT], triphasic dynamic contrast-enhanced magnetic resonance imaging [MRI] and contrast-enhanced ultrasonography) with serum α-fetoprotein (AFP) ≥400 ng/mL.

2. All patients must provide at least 1 archival tumor specimen. If archival tumor specimen is no longer available, *de novo* tumor biopsy will be required during screening.

3. HCC not amenable to local therapy.

4. Measurable disease according to RECIST v. 1.1.

5. Child-Pugh Class A disease (see Appendix 2). Score for hepatic encephalopathy must be 1; ascites score must be ≤2.

6. Barcelona Clinic Liver Cancer (BCLC) stage B or C disease. Stage B disease must be unresectable, not amenable to local therapy or refractory to local therapy.

7. No evidence of uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be ≤140 mm Hg, and the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

8. Age ≥20 years.

9. ECOG performance status 0 or 1.

10. Estimated life expectancy of at least 3 months.

11. Required baseline laboratory data within the following parameters:

    - Neutrophils ≥1,500/μL;
    - Platelets ≥75,000/μL;
    - Hemoglobin ≥9.0 g/dL;
    - Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤5 × ULN;

- Estimated creatinine clearance ≥50 mL/min as calculated using the Cockcroft Gault (CG) equation;
- INR <1.7 or prothrombin time (PT) <4 seconds above ULN (ie, Child-Pugh Score is no greater than 1);
- Serum albumin ≥2.8 g/dL (ie, Child-Pugh Score is no greater than 2);
- Total bilirubin ≤3 mg/dL (ie, Child-Pugh Score is no greater than 2);
- Urinary protein <2+ by urine dipstick. If dipstick is ≥2+ then a 24 hour urine collection should be done and the patient may enter only if urinary protein is <2.0 g per 24 hours.

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

13. Serum or urine pregnancy test (for females of childbearing potential) negative at screening.

    Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure.

    All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

14. 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 30 days after the last dose of assigned treatment.

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

16. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

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

1. Prior systemic treatment for advanced HCC, including prior treatment with approved or investigational drugs.

    - Prior immunotherapy with 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 sorafenib as well as any prior therapies with other VEGF pathway inhibitors.

2. Any prior locoregional therapy (such as hepatic arterial embolization, TACE, hepatic arterial infusion, radiofrequency ablation, percutaneous ethanol injection or cryoablation) within 4 weeks and radiotherapy or surgical procedure within 2 weeks (4 weeks for major surgery) of enrollment . Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to enrollment.

3. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade >1); however alopecia, sensory neuropathy Grade ≤2, or other Grade ≤2 AEs not constituting a safety risk based on investigator's judgment are acceptable.

4. 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 starting the study treatment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

5. Presence of hepatic encephalopathy (ie, Child-Pugh score of 2 or 3) and/or clinically relevant ascites (ie, Child-Pugh score of 3).

6. Presence of **main** portal vein invasion by HCC (invasion to 1st or 2nd branch of portal vein is acceptable).

7. NCI CTCAE Grade ≥3 hemorrhage within 4 weeks of enrollment, or variceal hemorrhage of any grade within 12 months of enrollment.

8. Evidence of inadequate wound healing.

9. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days of enrollment.

10. Any of the following within the 12 months prior to enrollment: 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.

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

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

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

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

15. Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v. 4.03 Grade ≥3).

16. Current use of immunosuppressive medication at the time of enrollment, except the following: a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

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

18. Active infection requiring systemic therapy except for hepatitis C virus (HCV) and hepatitis B virus (HBV) as follows:

    - Patients with chronic infection by HCV are eligible for study participation.

    - Patients with chronic infection by HBV are eligible for study participation only if they are on antiviral therapy and the infection is controlled by treatment prior to enrollment.

19. Administration of a live vaccine within 28 days prior to enrollment.

20. Current use or anticipated need for treatment with botanical formulation having an approved indication for liver cancer treatment, such as “Kanglaite”

21. 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 starting the study treatment (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.

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

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

24. 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 unless the ulcer is completely healed as confirmed by endoscopy prior to study treatment;
    - Active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    - Malabsorption syndromes.

25. Prior organ transplantation including allogenic stem-cell transplantation

26. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.

27. Diagnosis of any other malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration), or pathologically diagnosed in situ gastric (T1 [M]; UL [-]), esophageal (TIS or T1a), or colorectal cancer (Stage 0 [M]) treated with curative resection.

28. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or

patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

29. Participation in other studies involving investigational drug(s) within 4 weeks prior to enrollment.

30. Concurrent colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis

31. Other acute or chronic medical 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.

32. Pregnant female patients; breastfeeding female patients.

4.3. Lifestyle Requirements

4.3.1. Contraception

In this study, fertile male patients and female patients who are of childbearing potential as applicable to the study will receive avelumab for which the teratogenic risk is currently unknown in combination with axitinib, which has been associated with demonstrated teratogenicity. Patients who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 30 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the patient of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the patient or partner.

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the patient or male patient's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

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

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

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

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

4.4. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list 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 product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator 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 investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator 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/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For this study, the investigational products are avelumab and axitinib.

5.1. Allocation to Treatment

All patient will be assigned to starting dose of avelumab 10 mg/kg Q2W plus axitinib 5 mg BID after patients have given their written informed consent and have completed the necessary baseline assessments. The site staff will fax or e-mail a complete Registration Form to the designated sponsor study team member or designee. The sponsor will assign a

patient identification number and supply this number to the site. The patient identification number will be used on all study-related documentation at the site.

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

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

5.2. Patient Compliance

For self-administration of axitinib at home, compliance will be captured and completed by the patient with recording every dosing to a patient diary. The diary will be maintained by the patient to include missed or changed axitinib doses. Patients will be required to return all bottles of axitinib after at least every other cycle.

All doses of avelumab will be administered by the appropriately designated study staff at the investigator site.

5.3. Investigational Product Supplies

Avelumab and axitinib 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.

5.3.2. Preparation and Dispensing

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

5.3.2.1. Avelumab

Avelumab will be 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 interactive response technology (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.

5.4. 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 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.

Sites should make every effort to target infusion timing to be as close to 1 hour as possible. The exact duration of infusion should be recorded in both source documents and Case Report Form (CRF).

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every cycle. If the patient experienced either a weight loss or gain >10% compared to the weight used to calculate the prior dose, the amount of study drug required for preparation and administration for the current treatment must be recalculated using this most recent weight obtained.

Avelumab dose reduction for toxicity management is not permitted, however next administration may be omitted due to persisting toxicity or treatment may be discontinued as described in Table 2 and Section 5.4.5. Possible modifications of the infusion rate for the management of infusion-related reactions related to avelumab are described in Section 5.4.5.5.

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

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

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

Patients experiencing toxicity may require treatment adjustment or discontinuation according to the guidelines specified in Table 1 and Table 2.

5.4.3. Treatment After Initial Evidence of Radiologic Disease Progression

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

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

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

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

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

If the repeat imaging confirms PD, patients should be discontinued from study treatment. However, according to the investigator's clinical judgment and after discussion between the investigator and the sponsor, if a patient with evidence of PD is still experiencing clinical

benefit, the patient may be eligible for continued treatment with single agent avelumab, axitinib, or avelumab combined with axitinib. The investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

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

5.4.4. 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]).

5.4.5. Recommended Dose Modifications

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

In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom. In addition to dose modifications, investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

For avelumab, no dose modifications are permitted in this study, but next infusion may be omitted based on persisting toxicity, as outlined in Table 2. 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 dose level for intrapatient dose modification is listed in Table 1.

5.4.5.1. Intrapatient Axitinib Dose Escalation and Dose Reduction

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 blood pressure [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 2. 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.

5.4.5.2. Management of Axitinib-Related Hypertension

Patients will be issued BP cuffs (provided by the sponsor) for home monitoring and instructed to measure their BP at least once daily (before taking the morning dose of axitinib). 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.[32,33] 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 dihydropyridine (DHP) calcium channel blockers, etc.).[32,33]

Dose modification for axitinib in case of hypertension is described in Table 2.

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

Recommended axitinib dose modifications and avelumab infusion omissions in case of drug related toxicity are shown in Table 2. 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.

Table 2. 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 or if the same Grade 3 toxicity recurs (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 or urine protein creatinine (UPC) ratio. Dosing may continue while waiting for test results		
	<2 g proteinuria/ 24 hour or UPC <2	• Continue at the same dose level.	

Table 2. 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 or UPC ≥2	• Withhold until proteinuria is <2 g/24 hours or UPC <2. • Repeat 24-hour urine collection or UPC for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria is <2 g/24 hours or UPC <2. • 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 5.4.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
	2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	• If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and continue at the same dose level. • If on maximal antihypertensive treatment, reduce by 1 dose level. • See Section 5.4.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 2. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
	2 systolic BP readings separated by at least 1 hour show systolic pressure >160 mm Hg OR 2 diastolic BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	• Withhold until BP is less than 150/100 mm Hg and adjust antihypertensive medication. • Then, reduce by 1 dose level and resume treatment. • 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 5.4.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
	Recurrent hypertension following previous dose reduction (2 systolic BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) OR Recurrent diastolic BP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	• Repeat dose reduction by one lower dose level. • See Section 5.4.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 2. Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
Infusion-related Reaction	Grade 1-4	• Continue at the same dose level.	• See Sections 5.4.5.5 and 5.4.5.6 and Table 3.
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 5.4.5.7 and Table 4.
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
	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 or if the same Grade 3 toxicity recurs (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).
	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.

5.4.5.4. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion-related reactions, patients have to be premedicated approximately 30 to 60 minutes prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Premedication will include an antihistamine (for example, 25-50 mg diphenhydramine IV or oral equivalent), and paracetamol (acetaminophen) (eg. 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate, however, the prophylactic administration of systemic corticosteroids is not permitted.

Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. Patients should be instructed to report any delayed reactions to the investigator immediately.

Treatment recommendations for the management of infusion-related reactions and severe hypersensitivity reactions are outlined in Sections 5.4.5.5 and 5.4.5.6, 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 5.4.5.7.

5.4.5.5. Management of Avelumab Infusion-Related Reactions

Since avelumab is administered IV, infusion-related reactions may occur. Symptoms of infusion-related reactions include but are not limited to fever, chills, flushing, hypotension, dyspnoea wheezing, back pain, abdominal pain, and urticaria. Management of infusion-related reactions should follow the guidelines set forth in Table 3.

Table 3. 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 avelumab 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 recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect 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.

5.4.5.6. Management of Avelumab-related Severe Hypersensitivity Reactions

As with all monoclonal antibody therapies, there is a risk of severe hypersensitivity 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, epinephrine, allergy medications, bronchodilators, and oxygen should be available for immediate access.

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice.

Additional treatment recommendations for symptoms of avelumab infusion-related reactions are provided in Appendix 5 and may be modified based on local treatment standards and guidelines, as appropriate.

5.4.5.7. 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 4:

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

Some potential immune-related adverse events described with anti-PD-L1 monoclonal antibodies such as avelumab may overlap with some 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 5.4.5.7.

For overlapping potential immune-related toxicities, follow the specific management recommendations described in Table 4.

Table 4. 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 (e.g. 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 IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists >1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering >30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**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	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:

	for opportunistic infections Consider bronchoscopy, lung biopsy	Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 × ULN and/or Total bilirubin > ULN to 1.5 × 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 × ULN and/or total bilirubin > 1.5 to ≤3 × 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 × ULN and /or total bilirubin >3 × 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 × 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 × ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 × 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 (e.g. 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 (e.g. azathioprine, cyclosporine A).

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. 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	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.

	endocrinopathies (i.e. hypopituitarism/hypophysitis)	
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab

		therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	

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

See the IP manual for storage conditions of the product once reconstituted and/or diluted (for avelumab only).

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All bottles of study drug must be returned to the investigator by the patient at every other cycle and at the end of the trial.

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 investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

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

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

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

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

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

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

Recommended medications to treat infusion-related reactions, hypersensitivity reactions, and immune-related events are reported in Section 5.4.5.5, Section 5.4.5.6, and Section 5.4.5.7, 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.

The concomitant use of strong CYP3A4/5 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir,

telithromycin, and voriconazole) should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although axitinib dose adjustments have not been studied in patients receiving strong CYP3A4/5 inhibitors, consider a dose reduction if axitinib must be dosed with a CYP3A4/5 inhibitor.

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

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

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

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.[34]

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.

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 through end of treatment) if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should also be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression. Investigators may 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 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.

- Live vaccine within 28 days prior to study entry and during the study.

- 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.

- Other experimental pharmaceutical products.

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

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[35,36] 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.[37] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions treatment of irAEs, steroids are permitted according to the modalities indicated in Table 4.

- 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 4.

- 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

CCI [redacted] The biopsy sample(s) should be formalin-fixed and paraffin-embedded and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. Archived or *de novo* tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

CCI [redacted]

6.2. Study Period

For study period procedures, see SOA and Assessments section (Section 7). CCI [redacted]

6.2.1. Follow-up Visits

For Follow-up procedures, see SOA and Assessments section (Section 7). In this study, all patients must be followed-up for 90 days after the last dose of study treatment. After completion of Short-term follow-up, all patients will be followed every 3 months for survival (Long-term follow-up). Contact with the patient may be done via a phone call.

6.3. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost

to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single-agent avelumab or axitinib, or with avelumab in combination with axitinib, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.4.3);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the sponsor) may continue treatment with the other study treatment;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

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

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient 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 that 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 manner.

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs and physical examination, Electrocardiogram (ECG, 12-lead), LVEF by MUGA scan or Echocardiogram, laboratory assessments, including pregnancy tests, and verification of concomitant medications.

Safety will be monitored at regular intervals throughout the study as described in the SOA.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting administration of study treatment—once at the start of screening and once at the baseline visit, immediately before starting the study treatment(s). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit before the patient may receive the study treatment(s). Pregnancy tests will be repeated at every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study for survival follow-up.

7.1.2. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the SOA and analysed 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 5

Table 5. 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 or UPC	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		PTT or aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils or %	Sodium*			
Absolute Lymphocytes or %	Potassium*			
Absolute Monocytes or %	Magnesium*			
Absolute Eosinophils or %	Chloride*			
Absolute Basophils or %	Total Calcium*			
	Total Bilirubin* °			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Phosphorus or Phosphate*			
	Albumin			
	Total Protein			
	Uric Acid			
	Amylase			
	Gamma glutamyl transferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase			
	Triglycerides			
	HBV, HCV tests**			
	Thyroid Function Tests: TSH, free T4			
	Other Tests: ACTH, α-fetoprotein (AFP), PIVKA-II			

°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.

**HBV, HCV tests: The patients with chronic infection by HBV or HCV will be monitored viral status per standard practice of the study site.

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, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PIVKA-II=protein induced by Vitamin K absence or antagonists-II, TSH=thyroid-stimulating hormone, UPC=urine protein creatinine, WBC=white blood cell

7.1.3. Physical Examinations and Vital Signs

Physical examinations will be performed according to institutional guidelines on study days as described in the 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 SOA. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes. Two blood pressure readings will be taken at least 1 hour apart at each clinic visit. In addition, all patients will be monitoring BP at home as described in Section 5.4.5.2.

7.1.4. (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 creatine kinase [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 AEs. 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 assessments.

7.1.5. Left Ventricular Ejection Fraction by MUGA scan or Echocardiogram

For the evaluation of LVEF, both MUGA and Echocardiogram are acceptable. The same technique used at screening must be consistently used for the following assessments throughout the study.

7.2. Pharmacokinetics Assessments

7.2.1. Blood Sample Collection for Pharmacokinetic Analysis

Blood samples for axitinib PK and avelumab PK will be collected as outlined in the 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.

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.

7.2.2. Collection of Axitinib Pharmacokinetic Samples

At each time point for axitinib, a 3 mL whole blood sample will be collected into an appropriately labeled K_3 EDTA tube to provide a minimum of 1 mL plasma for axitinib PK analysis.

7.2.3. Collection of Avelumab Pharmacokinetic Samples

A 3.5 mL whole blood will be collected into a Serum Separator Tube (SST) at the designated times to provide serum for avelumab PK analysis.

7.3. Immunogenicity Assessment

A 3.5 mL 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. ADA sample at 30 day follow up is collected at 30 days after end of treatment of avelumab regardless of continuation of axitinib therapy. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.4. Translational and Pharmacodynamic Assessments

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

CCI [redacted]

Optional tumor biopsies obtained upon disease progression (End of Treatment) may be assessed relative to the mandatory pre-treatment biospecimens to examine tumoral and immunological changes which may occur over the course of therapy, including acquired mechanisms of resistance. Only core needle, excisional biopsies, or resection specimens are suitable. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Study Manual.

CCI [redacted]

[redacted]

CCI

CCI

[redacted]

[redacted]

CCI [redacted]

[redacted]

7.6. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans; it may also include brain CT or MRI scan at baseline and whenever brain metastases are suspected. The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons.

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

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, and every 8 weeks thereafter until confirmed PD per RECIST v1.1. If a patient discontinues the study treatment due to a reason other than disease progression, tumor assessments should be conducted until confirmed disease progression or initiation of new anticancer treatment, whichever come first. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration) and at the time of withdrawal from the treatment (if not done in the previous 8 weeks). CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. If radiological imaging shows PD, then tumor assessment should be repeated after at least 4 weeks to confirm PD, unless clinical deterioration occurs. See the SOA and Section 5.4.3 for treatment after initial evidence of disease progression.

Brain CT or MRI scans are required at baseline and when there is a suspected brain metastasis. Bone scan (bone scintigraphy) or 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET/CT) is required at baseline then every 12 weeks only if bone

metastases are present at baseline. Otherwise, bone imaging is required only if new bone metastases are suspected and at the time of confirmation of CR for patients who have bone metastases.

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

Assessment of response will be made using RECIST v. 1.1 (Appendix 3)[redacted]

All patients' radiologic images should be submitted for potential peer review by a third party.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details On Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the

investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and 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 recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified 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 recording as an AE.

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection 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 active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

8.2.4. 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 is 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 a persistent pretreatment laboratory abnormality);

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

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

8.3. Severity Assessment

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

The patient should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

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

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

- 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 patient or patient's partner becomes or is found to be pregnant during the patient's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety 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 Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as 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 sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the 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.

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a patient enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving patient exposure to the investigational product;

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

The full analysis set and the safety analysis set will be assessed. These analysis sets are identical. These analysis sets include all enrolled patients who receive at least 1 dose of study drug (avelumab or axitinib). Analyses will be conducted by dose cohort if lower dose of the combination (avelumab 10 mg/kg IV Q2W plus axitinib 3 mg BID) will be evaluated with adding cohort of patients.

9.1. Sample Size Determination

This study will enroll 20 patients to evaluate overall safety and tolerability with combination of avelumab plus axitinib. A sample size of 20 patients will provide at least 88% probability to observe at least one AE if the true incidence of the AE in the population is 10% or more.

9.2. Efficacy Analysis

In this study, assessment of antitumor activity is a secondary objective. Efficacy analyses will be presented in the form of statistical summaries and data listings. Efficacy endpoints will be defined based on **'start date'** which is the start date of study treatment.

9.2.1. Analysis of Secondary Endpoints

Efficacy data will be analyzed based on the full analysis set.

TTP is defined as the time from start date to the date of the first documentation of objective PD. TTP data will be censored on the date the last adequate tumor assessment for patients without PD, for patients who start new anti-cancer treatment prior to PD, for patients who die without PD, or for patients with PD after ≥2 missing tumor assessments. Patients who do not

have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the start date.

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

OR is defined as CR or PR according to RECIST v. 1.1 from the start date until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. Patients who do not have an on-treatment radiographic tumor assessment due to early disease progression, who receive anti-tumor treatments other than the study treatments prior to achieving CR or PR, or who die, experience disease progression, or drop out for any reason prior to achieving CR or PR will be counted as non-responders in the assessment of OR. OR rate (ORR) is defined as the proportion of patients who have an OR.

DC is defined as OR (CR or PR) or stable disease (SD) per RECIST v. 1.1 from the start date until the first documentation of objective disease progression or death due to any cause. DC rate (DCR) is defined as the proportion of patients with DC.

TTR is defined as the time from start date to the first documentation of objective tumor response (CR or PR) that is subsequently confirmed. DR and TTR will only be summarized among patients with confirmed response.

DR is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. The censoring rules for DR are same as for the definition of PFS.

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

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

CCI [redacted]

[redacted]

9.3. Analysis of Other Endpoints

9.3.1. Analysis of Secondary Endpoints

9.3.1.1. Pharmacokinetic Analysis of Avelumab and Axitinib

Axitinib C_{trough} (concentration at pre dose of axitinib) and C_{max} (concentration at 2-hour post dose) 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} (concentration at pre dose of avelumab) and C_{max} (concentration at end of infusion) plasma concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by 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.

All the concentration data will be listed but for summarization of C_{trough} and C_{max}, the concentrations deviated more than 20% from the planned time will not be included.

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 data may be combined with the data in other aveluab protocol for the analysis. The results of these modeling analyses may be reported separately from the clinical study report.

9.3.1.2. Immunogenicity Assessment

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

CCI [redacted]

CCI [redacted]

9.4. Safety Analysis

Summaries and analyses of the safety endpoint will be based on the safety analysis set.

9.4.1. Analysis of Primary Safety Endpoints

9.4.1.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v. 4.03 whenever possible. 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 v. 4.03 severity grade, and will be summarized by cycle and by relatedness to study treatment.

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v. 4.03 Grade≥3, trial drug-related events, and serious adverse events will be considered with special attention.

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

9.4.1.2. Laboratory Test Abnormalities

Laboratory test results will be graded according to the NCI CTCAE v. 4.03 severity grade. The frequency of patients with laboratory test abnormalities will be summarized according to the worst grade for each laboratory test.

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

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

9.4.2. Analysis of Other Safety Endpoints

Further details regarding other safety endpoints (definitions and analyses) will be provided in the SAP.

9.4.2.1. Electrocardiograms

ECG measurements will be used for the statistical analysis and all data presentations.

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, heart rate (HR), and RR, PR, QRS, QTc intervals. 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).

9.4.2.2. Vital Signs

Vital signs including blood pressure and pulse rate will be summarized using descriptive statistics. Any additional analyses of vital signs will be further detailed in the SAP.

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is a single-arm open-label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety and efficacy assessment, facilitating pharmacokinetics / pharmacodynamics modeling, and/or to support clinical development.

9.6. Data Monitoring Committee

This study will not use an external data monitoring committee.

Pfizer procedures for periodic safety review will be applied by an internal safety review team. Safety findings that have immediate implications for the management of patients on study will immediately be communicated to all investigators. Periodic safety review procedures will include:

- Monthly internal safety assessment including AEs, SAEs, Lab tests, vital signs, and ECG findings will be conducted.
- Discussions between the investigators and the sponsor of AEs, laboratory test abnormalities, vital signs, and ECG findings observed in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and to make risk/benefit assessments.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may

review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs 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 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 may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

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

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

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

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

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

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information 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 All Participating Countries

End of trial in all participating countries is defined as last patient last visit (LPLV).

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

Pfizer posts European Union (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 PCD for studies in adult populations or within 6 months of the PCD 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 the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI 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, patient to the other requirements of this section.

For all publications relating to the study, the 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. Child-Pugh Classification

Parameter	Point		
	1	2	3
Encephalopathy	None	Grade 1-2 (Moderate)	Grade 3-4 (Severe)
Ascites	Absent	Mild	Moderate
Prothrombin time prolonged (sec.) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8

Note: Patients in grayed-out portion of the table not eligible in this study

Class A: 5-6 points

Class B: 7-9 points

Class C: 10-15 points

Appendix 3. Response Evaluation Criteria in Solid Tumors Version 1.1

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

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 <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

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

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

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

Target Lesions

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

- 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 (i.e., 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 (e.g., '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 should be discussed with the radiologist and the Sponsor to determine if substitution is possible. If not, subsequent objective statuses are not evaluable.

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 Disease (SD): 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.
- Progressive Disease (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 (NE): Progression has not been documented, and
    - one or more target 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 (e.g., 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 (if being followed) above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Not evaluable (NE): Progression has not been determined and
    - one or more non-target lesion sites have not been assessed or
    - assessment methods were inconsistent with those used at baseline or
    - one or more non-target lesions cannot be assessed (e.g., 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 PD even after discontinuation of study 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 the following table.

Table 6. Objective Response Status at Each Evaluation for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or 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

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 7. Objective Response Status at Each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal progression	Yes or No	PD
Any	Yes*	PD

* New lesions must be unequivocal

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment/randomization until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after start of the treatment/randomization at a minimum interval of 8 weeks.

CCI [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted] if substitution is possible. If not, subsequent objective statuses are indeterminate.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted] orsening of the underlying chronic liver disease and be unrelated to cancer progression.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

Appendix 5. Treatment Recommendations for Symptoms of Avelumab Infusion-Related Reactions

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

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

- Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
- 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 (e.g, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.)

- Temporarily discontinue 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 avelumab infusion at 50% of previous rate as soon as infusion related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.

For Grade 3 or Grade 4 Symptoms: (Severe reaction; Grade 3: prolonged [e.g, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae [e.g, 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.

Appendix 6. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
AE	adverse event
AFP	α-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BBS	Biospecimen Banking System
BID	twice daily
BOR	best overall response
BP	blood pressure
CI	confidence interval
CK	creatine kinase
CR	complete response
CRF	case report form
CSA	clinical study agreement
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed and paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Conference on Harmonisation

Abbreviation	Term
ID	identification
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
irAE	immune-related adverse event
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LLN	lower limit of normal
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
CCI	[redacted]
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
N/A	not applicable
nAb	Neutralizing Antibody
NCI	National Cancer Institute
OR	objective response
ORR	objective response rate
OS	overall survival
PCD	primary completion date
PD	progressive disease
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOA	schedule of activities
SRSD	single reference safety document

Abbreviation	Term
TBili	total bilirubin
TTP	time to progression
TTR	time to tumor response
ULN	upper limit of normal
US	United States
UPC	urine protein creatinine