A PHASE 2, OPEN LABEL STUDY TO EVALUATE SAFETY AND CLINICAL ACTIVITY OF AVELUMAB (BAVENCIO®) IN COMBINATION WITH AXITINIB (INLYTA®) IN PATIENTS WITH ADVANCED OR METASTATIC PREVIOUSLY TREATED NON-SMALL CELL LUNG CANCER OR TREATMENT NAÏVE CISPLATIN-INELIGIBLE UROTHELIAL CANCER

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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	07 March 2018	The following change to the original protocol was requested by the US FDA: A footnote was added to Table 4, for guidance related to patients with non-small cell lung cancer (NSCLC) who may develop risk factors for pulmonary hemorrhage while on treatment. In addition, the following changes were implemented: Changes were made to the Schedule of Activities: To clarify that smoking history is being collected as part of the Medical/Oncological History and to clarify the time intervals for blood pressure and pulse readings. Section 5.5.5.2: Text updated for clarification that blood pressure monitoring devices will be provided to patients. Section 7.1.5: Text updated to clarify the time interval for blood pressure and pulse readings.
Original protocol	19 December 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Avelumab is a human immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against programmed death-ligand 1 (PD-L1). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint inhibition pathway. In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first treatment for metastatic Merkel cell carcinoma (MCC). In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Avelumab is currently being investigated as single agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies.

With evolving data it is becoming evident that combination immunotherapy strategies will be necessary to achieve enhanced anti-tumor activity for patients who do not experience disease control with single-agent immune checkpoint inhibitors.[1] Growing nonclinical and clinical evidence suggest that the combination of checkpoint inhibition plus anti-angiogenic agents may potentially improve anti-tumor activity and patient outcomes compared to results seen with single agents. Vascular endothelial growth factor (VEGF) can exert immunosuppressive effects in tumors by inhibiting maturation of dendritic cells, promoting immune suppressive cell infiltration and enhancing immune checkpoint molecule expression.[62] Likewise, immunosuppressive cells such as myeloid derived suppressor cells secrete pro-angiogenic factors VEGF and matrix metalloproteinase (MMP) which directly promote angiogenesis growth[63] and induce resistance to anti-VEGF therapy. Given the immunomodulatory and anti-angiogenic properties of anti-VEGF therapies, including axitinib,[62-66] potential synergy with anti-VEGF therapy in combination with immune checkpoint blockade may increase clinical efficacy in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior platinum-containing therapy, and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

Study Objectives

Primary Objective

- To evaluate the Objective Response Rate (ORR) based on Investigator assessment, per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

Secondary Objectives

To evaluate the following in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease:

- The safety and tolerability of avelumab in combination with axitinib;
- The anti-tumor activity of avelumab in combination with axitinib;
- The pharmacokinetics of avelumab and axitinib when administered in combination;
- Candidate predictive and/or early response biomarkers in pre-treatment tumor tissue and pre- and post-treatment blood samples that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib. Assessments may include but are not limited to tumor mutational burden, immune repertoire and PD-L1 expression within the tumor microenvironment;
- The immunogenicity of avelumab when combined with axitinib.

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Study Endpoints

Primary Endpoint

Confirmed Objective Response (OR) based on Investigator assessment per RECIST v1.1.[77]

Secondary Endpoints

- Adverse events (AEs) as characterized by type, severity as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03, (Appendix 2), timing, seriousness, and relationship to study treatments;

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;

- Time-to-event endpoints including time to tumor response (TTR), duration of response (DR), progression-free survival (PFS) based on Investigator assessment per RECIST v1.1, and overall survival (OS);

- Pharmacokinetic parameters including trough and maximum concentrations (C_{trough}, C_{max}) of avelumab and axitinib;

- Tumor tissue biomarker status (ie, positive or negative based on, for example, PD-L1 expression and/or quantitation of tumor mutational burden as well as characterization of the immune repertoire in peripheral blood and/or tumor);

- Anti-drug antibody (ADA) titers and neutralizing antibodies (NAb) against avelumab.

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Study Design

This is an open-label, multi-center, Phase 2 study to evaluate the safety and efficacy of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy, and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

Approximately 40 patients will be enrolled in each tumor cohort, NSCLC and UC.

Study Treatment

Avelumab 800 mg fixed dose will be administered as a 1-hour (hr) intravenous (IV) infusion every 2 weeks (Q2W), on Day 1 and Day 15 of each 28 day cycle.

Axitinib will be administered at 5 mg by mouth (PO) twice daily (BID), with or without food, on a continuous dosing schedule (see Section 5.5.2).

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.

Statistical Methods

The primary objective is to assess the ORR of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease. The primary endpoint is confirmed OR, which is defined as a complete response (CR) or partial response (PR) per RECIST v1.1 by Investigator from the first dose of study treatment until disease progression (PD) or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of treated patients with confirmed CR or PR per Investigator's assessment according to RECIST v1.1.

Approximately 40 patients will be enrolled from each of 2 tumor type cohorts: NSCLC and UC. Thus, a total of approximately 80 patients will be enrolled.

With 40 treated patients per tumor type cohort, ORR can be estimated with a maximum standard error of 0.079. Further, assuming beta (0.5, 0.5) prior:

- NSCLC cohort: if 15 responders (out of 40 patients, ORR of 37.5%) are observed, the probability of a true ORR ≥30% (considered a clinically relevant effect above single-agent checkpoint inhibition,[39-43] [Section 1.2.2]) will be ≥80% (85.0%).

- UC cohort: if 19 responders (out of 40 patients, ORR of 47.5%) are observed, the probability of a true response rate ≥40% (considered a clinically relevant effect above single-agent checkpoint inhibition,[25,26] [Section 1.2.1]) will be ≥80% (83.4%).

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 patient.

Visit Identifiers[1]	**Screening**	**Study Treatment (1 cycle = 28 days)**		**End of Treatment/Withdrawal**[3]	**Post-Treatment Follow-Up**	
		Cycle 1 and higher			**Short-Term**[4]	**Long-Term**[4]
	≤28 Days Prior to Enrollment	**Day 1**[2] **(±3 days for cycle ≥2)**	**Day 15 (±3 days)**		**Day 30, Day 60, Day 90 (±3 days)**	**Every 12 weeks (±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	
Contraception Check[9]	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
Vital Signs[10]	X	X	X	X	X	
Home Blood Pressure Monitoring[11]		X, continuously monitoring				
Laboratory Studies						
Hematology[12]	X	X	X	X	X	
Blood Chemistry[13]	X	X	X	X	X	
Coagulation[12]	X	X	X	X	X	
Thyroid Function Tests[14]	X	Cycle 1, then Q8W		X	X	
ACTH[15]	X	Cycle 1, then Q8W		X	X	
HBV, HCV Tests[16]	X	If clinically indicated				
Serum/Urine Pregnancy Test(*for women of childbearing potential only*)[17]	X	X		X	X	
Urinalysis[18]	X	If clinically indicated		X	If clinically indicated	
LVEF by MUGA Scan or Echocardiogram[19]	X	Cycle 2, then Q12W		X	X (Day 30 only)	
12-Lead ECG[20]	X	As clinically indicated		X		

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 28 days)		End of Treatment/Withdrawal[3]	Post-Treatment Follow-Up	
		Cycle 1 and higher			Short-Term[4]	Long-Term[4]
	≤28 Days Prior to Enrollment	Day 1[2] (±3 days for cycle ≥2)	Day 15 (±3 days)		Day 30, Day 60, Day 90 (±3 days)	Every 12 weeks (±14 days)
Disease Assessments						
Tumor Assessments[21]	X	Q8W after first dose of study drug for 1 year from start of study treatment, and then Q12W thereafter until PD regardless of discontinuation of study treatment or initiation of subsequent anti cancer therapy.				
Survival[22]					X	X
Other Clinical Assessments						
Follow-up for Axitinib Dosing Compliance[23]		X (D5 ±3 days)				
Concomitant Medications/Treatments[24]	X	X	X	X	X	
Adverse Events[25]		X, continuously monitored and recorded		X	X	
New Anti-cancer Therapy[26]					X	X
Enrollment/Study Treatment[27]						
Avelumab[28]		X	X			
Axitinib[28]		X(continuous daily dosing)				
Other Samplings						
Pharmacokinetics for axitinib[29]		X (Cycle 2 only)	X (Cycles 1 and 2)			
Pharmacokinetics for avelumab[30]		X (Cycle 1 and 2)	X (Cycles 1,3,6,9 and 12)			
[redacted] CCI		[redacted]				
Translational and Pharmacodynamic Biospecimens[32]	X	X (Cycles 1,2,3 and 4)		X		
Mandatory Archival or *de novo* FFPE Tumor Tissue[33]	X			X (optional)		
Anti-Avelumab Antibodies and Neutralizing Antibodies[34]		X (Cycle 1 and 2)	X (Cycles 1, 3, 6, 9, and 12)	X	X (Day 30 only)	
Saliva Sample[35]		X (Cycle 1 only)				

ACTH=adrenocorticotropic hormone; 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=multi-gated acquisition; 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 Day 1 of each cycle 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 anti-cancer treatment. Beyond the 90 days until the end of the study, all patients will be followed every 12 weeks (±14 days) for survival, and new systemic anti-cancer 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 therapy regimens, surgery, locoregional therapy, radiation therapy and smoking history.
7. **Baseline Signs/Symptoms:** To be recorded pre-dose 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:** See Section 4.3 and Section 7.1.1.
10. **Vital Signs:** Blood pressure and pulse rate should be taken with the patient in the supine or seated position after the patient has been lying down or sitting quietly for at least 5 minutes. Two blood pressure readings will be taken at least 1 hour apart at each clinic visit. See Section 7.1.5.
11. **Home Blood Pressure Monitoring:** All patients will receive home blood pressure monitoring devices and blood pressure will be monitored at home. See Section 5.5.5.2 for further details.
12. **Hematology and Coagulation**: Required tests are listed in Table 7. May also be performed when clinically indicated.
13. **Blood Chemistry:** Full chemistry panel (required tests are listed in Table 7) is required as follows: Screening, Day 1 of each Cycle, End of Treatment and Short-Term Follow-up. Core chemistry panel (required tests are listed in Table 7) is required as follows: Day 15 of each Cycle. May also be performed when clinically indicated.
14. **Thyroid Function Tests:** May also be performed when clinically indicated. See Table 7.
15. **ACTH:** May also be performed when clinically indicated. See Table 7.
16. **HBV, HCV Tests**: Performed at Screening and as clinically indicated.
17. **Serum/Urine Pregnancy Test** (*for women of childbearing potential only*): See Section 4.1 for criteria for defining women of non-childbearing potential. Results of the pregnancy test should be available prior to the beginning of each cycle. See Section 7.1.1.
18. **Urinalysis**: Required at Screening, at Cycle 1 Day 1, when clinically indicated 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. See Table 7.
19. **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.
20. **12-Lead Electrocardiogram (ECG)**: See Section 7.1.6 for details. ECG measurements will be obtained at Screening, as clinically indicated and End of Treatment. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history.

21. **Tumor Assessments**: Baseline scans must be performed within 28 days prior to first dose of study drug. Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, then every 8 weeks from first dose of study drug for 1 year from start of study treatment, and then every 12 weeks thereafter until PD regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy. See Section 7.6 for additional information.

22. **Survival:** All patients will be followed for survival and subsequent anti-cancer therapies every 12 weeks (±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.

23. **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.
24. **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.
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. See Section 8.1.4 for guidance on the time period for collecting and reporting AE and SAEs. If a patient begins a new anti-cancer 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 active collection period.
26. **New Anti-cancer Therapy:** If a patient begins a new anti-cancer 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.
27. **Enrollment:** Managed by an Interactive Response Technology (IRT) system operated by Pfizer, Inc. See Section 5.1 for information regarding the IRT system. Investigational product administration must begin within 3 calendar days after enrollment.
28. **Study Treatment:** Axitinib will be given orally (PO) twice daily (BID) on a continuous schedule. Avelumab will be given as a 1-hour (-10/+20 minutes) intravenous (IV) infusion every 2 weeks (see Section 5). Laboratory safety assessments must be performed and results reviewed by the treating physician prior to each study drug administration.
29. **Pharmacokinetics for axitinib:** PK samples for axitinib (3 mL) will be collected at pre-dose and 2-4 hours post-dose on Cycle 1 Day 15 and Cycle 2 Day 1 and Day 15. Details are outlined in Section 7.2.
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 on Cycle 1 Day 1 and Day 15, Cycle 2 Day 1. After that, trough (pre-dose) samples will be collected at Day 15 of Cycles 3, 6, 9, and 12. Pre-dose samples can be taken up to 2 hours prior to the start of avelumab infusion. Details are outlined in Section 7.2.

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32. **Translational and Pharmacodynamic Biospecimens:** CCI [redacted] One 10 mL of blood red-top serum BD Vacutainer® for serum preparation will be collected on Cycle 1, Day 1, pre-dose. See Section 7.4.
33. **Mandatory Archival or *de novo* FFPE Tumor Tissue:** See Section 6.1.1 and Section 7.4.1.
34. **Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (NAb):** One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Cycle 1 Day 1 and Day 15, Cycle 2 Day 1, and Day 15 of Cycles 3, 6, 9 and 12, End of Treatment, and Short Term follow up Day 30. All samples should be drawn within 2 hours before start of avelumab infusion. See Section 7.3.
35. **Saliva Sample:** Unless prohibited by local regulations or ethics committee decision, collect a saliva sample optimized for DNA analysis before the first dose of study drug treatment. See Section 7.4 and Laboratory Manual.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

The study will investigate avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy, and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

The mechanisms of action of each investigational product are described in Section 1.2.3 and Section 1.2.4.

1.2. Background and Rationale

1.2.1. Urothelial Cancer

UC includes tumors originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra.[2] Bladder cancer alone accounts for 90% of UC,[2] and is the ninth most prevalent cancer worldwide, with approximately 430,000 new cases diagnosed and 165,000 deaths attributed to this disease each year.[3-5] The incidence and mortality of bladder cancer have remained unchanged over the last 24 years.[6] Approximately 30% of patients with newly diagnosed UC present with muscle-invasive UC of the bladder,[7] a high-grade, typically aggressive disease requiring multimodal therapy including radical cystectomy and chemotherapy.[2,8,9] Metastatic disease is observed in 5% of patients at the time of diagnosis;[8] those patients who are diagnosed with localized muscle invasive tumor and treated with radical cystectomy alone usually develop metastatic disease within 2 years of the initial diagnosis.[10,11]

Combination chemotherapy with cisplatin-based regimens is the standard of care for first-line locally advanced or metastatic UC.[12-16] However, up to 50% of patients are ineligible or "unfit" to receive cisplatin due to age- or disease-associated renal dysfunction, poor performance status or other existing co-morbidities such as hearing loss, neuropathy and heart failure.[17-19] Standard treatment options for these treatment naïve, cisplatin-ineligible patients have included carboplatin-based regimens[20] and single- or double-agent chemotherapy depending on patient presentation and performance status.[21,22] While no direct comparison of cisplatin- versus carboplatin-based regimens has been conducted, only cisplatin containing regimens have shown survival benefit in patients with advanced or metastatic UC.[14-16,23,24] Cisplatin-based regimens have a median OS of 14-15 months[15,16] while gemcitabine plus carboplatin is associated with a median OS of 9 months and 21% treatment discontinuation due to treatment-related toxicity.[20] Consequently, due to the survival differences of the platinum-based regimens, there is an unmet medical need for improvements in clinical efficacy and treatment tolerability in cisplatin-ineligible for patients with advanced or metastatic UC.

Blocking the PD-1/PD-L1 pathway has shown therapeutic benefit for many tumor types, including UC. Remarkable breakthroughs in second-line systemic treatment have led to the approvals of five immune checkpoint (PD-1/PD-L1) inhibitors, including avelumab (Bavencio®), in the US and Europe (EU) for single agent use in patients with UC who have progressed during or following platinum-containing chemotherapy or progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.[2]

CCI [redacted] Please see Section 1.2.3.3 for detailed data with avelumab in patients with metastatic or locally advanced UC, who have progressed during or following platinum-containing chemotherapy or progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Furthermore, two immune checkpoint inhibitors, atezolizumab, PD-L1 mAb, (Tecentriq®) and pembrolizumab, PD-1 mAb, (Keytruda®), gained approval in the US and EU as single-agent, first-line therapy options for cisplatin-ineligible patients with advanced or metastatic UC.[25,26] Results from the IMvigor 210 cohort 1 (N=119 treated), a single-arm, Phase 2 study testing the safety and efficacy of atezolizumab monotherapy in patients with cisplatin-ineligible UC, showed an ORR of 23% (95% CI: 16-31%) and median OS of 15.6 months (95% CI: 10.4 months to not estimable).[26] The most common treatment-related AEs were fatigue (30%), diarrhea (12%) and pruritus (11%). In another Phase 2, single-arm study (KEYNOTE-052, N=370 treated), pembrolizumab monotherapy also showed anti-tumor activity and acceptable safety in patients with treatment naïve, cisplatin-ineligible UC.[25] ORR was 24% (95% CI: 20-29%) and 6 month OS rate was 67% (95% CI: 62-73%). Common treatment-related AEs included fatigue (15%), pruritus (14%) and rash (9%).

VEGF blockade has been extensively studied in first- and second-line UC.[27] To date, monotherapy studies, including tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib and sorafenib as well as aflibercept, an antibody-based VEGF recombinant fusion protein, have not shown single-agent clinical activity.[27] Combination studies with chemotherapy have been more encouraging though toxicity and tolerability concerns have adversely impacted risk/benefit considerations. Bevacizumab in combination with cisplatin- and carboplatin-based regimens both demonstrated impressive efficacy with median OS of 19.1 months and 13.9 months, respectively.[28,29] However, significant Grade ≥3 hematologic treatment-related toxicity in addition to vascular thrombotic events (VTE) were noted in both studies. Likewise, sunitinib in combination with cisplatin plus gemcitabine showed ORR ranging from 49 to 64% but was also poorly tolerated.[30,31] Conversely, pazopanib plus paclitaxel was studied in a heavily pretreated patient population (N=28 evaluable patients) where ORR was 54% (95% CI: 33.9-72.5%) with median PFS of 6.2 months and median OS 10.0 months and was generally well-tolerated.[32] The most common Grade ≥3 AEs were fatigue (13%) and anemia (13%). Most recently, results from the Phase 3 study (RANGE) testing ramucirumab, a vascular endothelial growth factor receptor-2 (VEGFR-2) antibody, plus docetaxel compared to placebo plus docetaxel in previously treated patients with UC were reported by Petrylak et al at the European Society for Medical Oncology (ESMO)

2017 annual meeting. A statistically significant improvement was observed for PFS, median 4.07 months vs 2.76 months, respectively, (hazard ratio [HR]=0.757, 95% CI: 0.607–0.943, p=0.0118), thus potentially providing another therapy option for second-line UC.[33]

1.2.2. NSCLC

NSCLC is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative.[5,34] Standard therapy in later stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy or immunotherapy.[35,36] Targeted therapies such as TKIs may be used for appropriate patients. In spite of these treatments, 5-year survival is only about 17.0% for advanced-stage NSCLC patients, highlighting the need for novel therapies and treatment regimens.[37]

Single-agent chemotherapy has been the standard of care for second- and third-line therapy for patients with advanced NSCLC in whom prior platinum-based therapy failed.[37,38] However, a new treatment paradigm has emerged based on five randomized studies that evaluated immune checkpoint inhibitor monotherapy compared to single-agent chemotherapy.[39-43] Results across these studies consistently demonstrated clinically meaningful improvements in OS with medians ranging from 9.2 to 13.8 months for checkpoint inhibitors versus 6.0 to 9.6 for chemotherapy.[39-43] ORR ranged from 14% to 20% and importantly, extended duration of response was observed varying from 14.3 -17.2 months to not reached (NR) compared to 5.6 to 8.4 months for chemotherapy. Efficacy was independent of PD-L1 expression though trends toward greater benefit were seen among higher levels of PD-L1 expression. Both squamous and nonsquamous histologies derived clinical benefit. Safety profiles were consistent among the trials with low grade (Grade 1 or 2) fatigue, nausea and decreased appetite being the most commonly reported AEs.[39-43] In addition, substantially fewer treatment-related Grade ≥3 AEs and treatment-related discontinuations were reported, indicating single agent checkpoint inhibitors are generally well tolerated and the AE profile is quite different compared with chemotherapy. Indeed, a recent updated 2-year safety and survival analysis from the CHECKMATE 017 and 057 studies showed long-term benefit with nivolumab compared to docetaxel in squamous cell histology, 2-year OS rate of 23% (95% CI, 16-30%) versus 8% (95% CI, 4-13%) and nonsquamous histology, 2-year OS rate of 29% (95% CI, 24-34%) versus 16% (95% CI, 12-20%).[44] No new safety signals were identified.

Anti-angiogenic therapy has demonstrated anti-tumor activity in advanced NSCLC. Bevacizumab (Avastin®), a mAb targeting VEGF, was the first approved anti-angiogenic agent in advanced NSCLC for front-line therapy in combination with chemotherapy based on the Eastern Cooperative Oncology Group (ECOG) 4599 trial which compared bevacizumab plus paclitaxel/carboplatin vs paclitaxel/carboplatin alone in treatment naïve patients with nonsquamous histology.[45] Significant improvements in PFS (median 6.2 months vs 4.5 months, HR= 0.66, p<0.001), response rate (RR) (35% vs 15%, p<0.001) and OS (median 12.3 months vs 10.3 months, HR= 0.79, p=0.003) were observed in the bevacizumab arm versus chemotherapy arm. The experimental regimen was well-tolerated though higher rates of Grade ≥3 bleeding were observed in the bevacizumab arm compared to the

chemotherapy doublet, (4.4% vs 0.7%, p<0.001). Subset analyses from an earlier Phase 2 study with bevacizumab plus paclitaxel/carboplatin identified clinical features such as squamous histology, cavitary tumors and centrally located tumors with close proximity to major blood vessels as risk factors for life-threatening bleeding and as a result, were excluded in later bevacizumab trials.[46] Ramucirumab (Cyramza®), a mAb targeting VEGRF-2, was recently approved in combination with docetaxel for second-line treatment of NSCLC based on results from the REVEL study.[47] In this Phase 3, randomized, double-blind study, ramucirumab plus docetaxel was compared to docetaxel/placebo in patients who progressed during or after a platinum-doublet regimen; both squamous and nonsquamous histologies were included. Median OS in the ramucirumab arm was 10.5 months versus 9.1 months for the placebo arm (HR, 0.86; 95% CI: 0.75-0.98; p=0.023).[47] The most common Grade ≥3 AEs were hypertension, fatigue and hematologic neutropenia, febrile neutropenia and leukopenia. Though the ramucirumab arm had more bleeding/hemorrhage events of any grade compared to the placebo arm (29% vs 15%), the number of Grade ≥3 events were the same in both arms.

Recent data also demonstrated anti-tumor activity of anti-angiogenic TKIs in patients with advanced NSCLC.[48] In a Phase 3 (LUME-Lung1), randomized, double-blind study, nintedanib, a multi-kinase TKI with anti-VEGFR-2, fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) α and β activity, was evaluated in combination with docetaxel compared to placebo/docetaxel in second-line patients with advanced NSCLC.[49] PFS, the primary endpoint, was significantly improved in the nintedanib arm compared to the placebo arm, median 3.4 months versus 2.7 months (HR=0.79, 95% CI: 0.68-0.92, p=0.019). In pre-specified sub-group analyses, OS was significantly improved in the nintedanib combination for all patients with adenocarcinoma histology compared to placebo, median 12.6 months versus 10.3 months (HR=0.83, 95% CI: 0.70-0.99, p=0.0359) and for patients with adenocarcinoma who progressed within 9 months after starting first-line treatment, median 10.9 months compared to 7.9 months (HR=0.75, 95% CI: 0.60-0.92, p=0.0073).[49]

Clinical experience with axitinib in NSCLC is described in Section 1.2.5.

1.2.3. Avelumab (BAVENCIO®, MSB0010718C)

Avelumab (MSB0010718C) is a human Ig G1 mAb directed against PD-L1. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1, thereby interfering with this key immune checkpoint inhibition pathway. For complete details of the in vitro and nonclinical studies, refer to the avelumab Investigator's Brochure (IB).[50]

1.2.3.1. Avelumab Clinical Experience

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 adult cancers, including NSCLC, gastric cancer, Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), ovarian cancer, UC, head and neck cancer, classic Hodgkin's Lymphoma and non-Hodgkin's Lymphoma, as single agent or in combination with chemotherapy, TKIs, or other immune-modulating agents.

On 23 March 2017, avelumab received accelerated approval from the FDA for the treatment of adults and pediatric patients 12 years and older with metastatic MCC, including those who have not received prior chemotherapy. In addition, on 09 May 2017, avelumab was also approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy, or who experience disease progression with 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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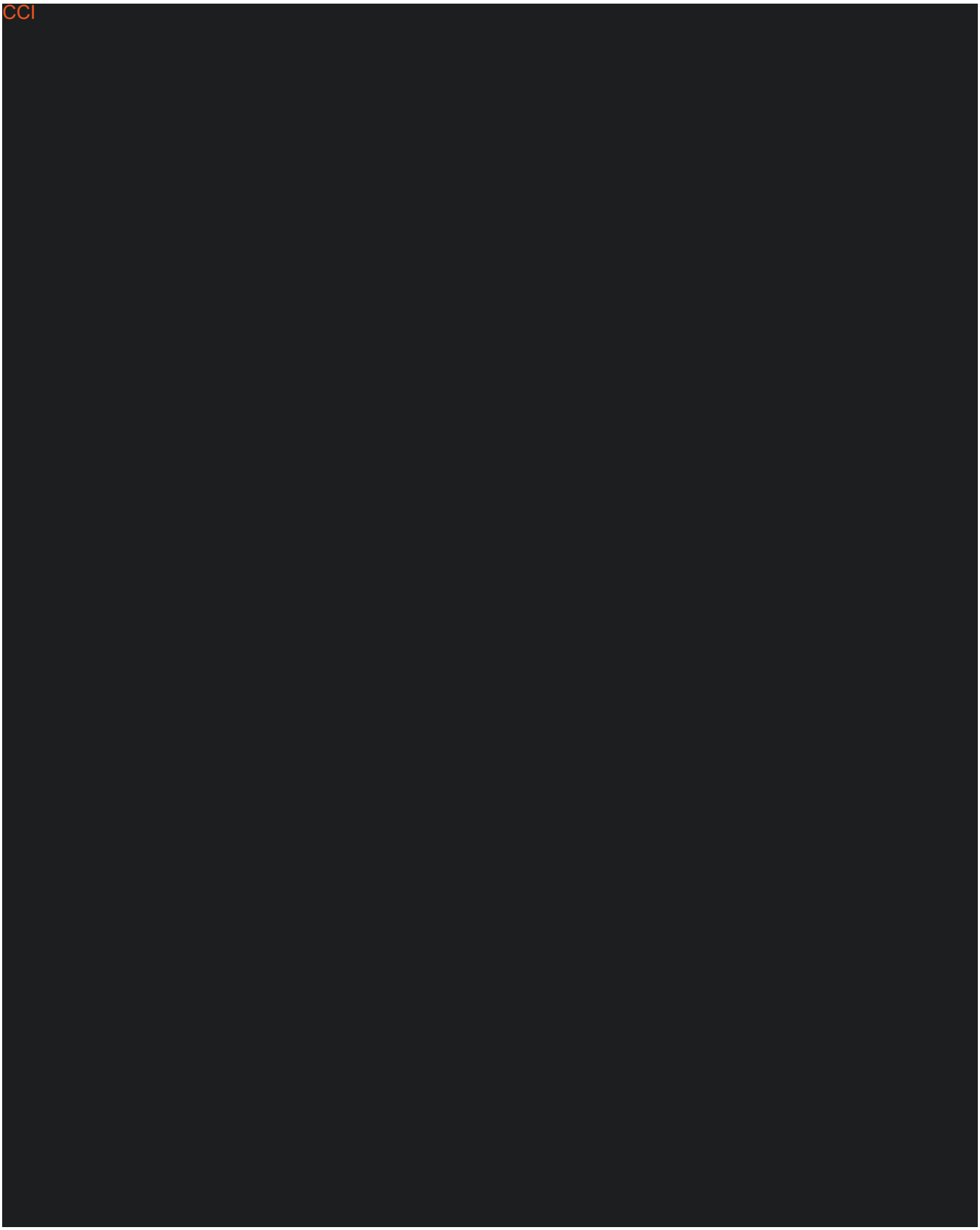

1.2.3.3. Clinical Experience in Patients with Locally Advanced or Metastatic UC

On 09 May 2017, avelumab received FDA approval for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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1.2.3.4. Pharmacokinetics of Avelumab Fixed Dosing

To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg every 2 weeks (Q2W) to more than 1700 patients across multiple indications. Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for monoclonal antibodies, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body-weight independent) dosing regimens.[53-55] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population pharmacokinetic (PK) analysis was conducted based on the acquired data across 3 single-agent avelumab studies in 1827 patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are similar, less variable with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the population median weight. Low-weight subjects tended toward marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when fixed dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, the 800 mg Q2W dosing regimen is expected to result in C_{trough} >1 μg/mL required to maintain avelumab serum concentrations at >90% target occupancy (TO) throughout the entire Q2W dosing interval in all weight categories.

Therefore, in this clinical trial, a fixed dosing regimen of 800 mg administered as a 1-hour IV (-10 min/+20 min) infusion will be utilized for avelumab on Days 1 and 15 of each cycle.

Complete information for avelumab may be found in the SRSD, which for this study is the avelumab IB.[50]

1.2.4. 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).[56]

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-TAG2 transgenic mice model and demonstrated anti-tumor efficacy including marked cytoreductive anti-tumor 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. Following twice daily oral administration, axitinib is rapidly absorbed (median T_{max} 2.5-4.1 hours). The plasma half-life of axitinib ranges from 2.5 to 6.1 hours and steady state is expected within 2 to 3 days of dosing. Dosing of axitinib at 5 mg twice daily resulted in approximately 1.4 fold accumulation compared to administration of a single dose. At steady state, axitinib exhibits approximately linear 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.[57]

1.2.5. Clinical Experience with Axitinib in NSCLC

Axitinib has been evaluated in NSCLC as monotherapy and in combination with platinum- and taxane-based regimens.[58,59] In Schiller et al, axitinib single-agent activity was evaluated in a Phase 2, open-label study among 32 patients with squamous or nonsquamous histology; 23 patients had received ≥1 previous systemic therapy. Axitinib was well-tolerated and demonstrated preliminary single-agent activity with an ORR of 9%, a disease control rate of 41% and median OS of 14.8 months (95% CI: 10. 7 months-not estimable).[59] The most common treatment-related events were fatigue, anorexia, diarrhea, nausea and hypertension. In a Phase 1 dose escalation study, axitinib at 5 mg BID was examined in combination with cisplatin- and carboplatin-based regimens among patients with advanced solid tumors. A total of 17 patients with NSCLC, including a squamous cell expansion cohort, received the axitinib plus carboplatin-based regimen; objective responses were observed in 5 patients with NSCLC.[58] No Grade ≥3 events of hemoptysis were noted.

In a Phase 2, open-label, single-arm study, 38 first-line patients with squamous cell NSCLC were treated with six cycles of axitinib plus cisplatin-based regimen and continued on maintenance axitinib monotherapy.[60] ORR was 39.5% and median OS was 14.2 months. The most frequent Grade ≥3 AEs were hypertension, neutropenia, fatigue and anemia. Pulmonary hemorrhage was observed in 3 patients including one Grade 5 event.

In another Phase 2 study, 170 treatment naïve patients with nonsquamous cell NSCLC were randomized to receive axitinib/pemetrexed/cisplatin, modified axitinib dosing/pemetrexed/cisplatin or pemetrexed/cisplatin alone.[61] Although axitinib arms did not show a statistically significant difference in ORR, it was numerically higher in the axitinib arms compared to chemotherapy alone, 45.5% for the standard axitinib arm, 39.7% in the modified axitinib dosing arm and 26.3% for the pemetrexed/cisplatin arm; median OS was 17.0 months, 14.7 months and 15.9 months, respectively. Gastrointestinal AEs (vomiting, nausea), fatigue and neutropenia were common among all treatment arms.
Grade ≥3 hypertension was observed in the axitinib arms and Grade ≥3 fatigue in the chemotherapy alone arm.

1.2.6. Clinical Experience of Combination Therapy of Avelumab Plus Axitinib

Study B9991002 is a Phase 1b, open-label, multicenter, multiple-dose trial of the combination of avelumab with axitinib in treatment-naïve patients with aRCC. A dose-finding phase preceded the dose-expansion phase of the trial. The study objectives were to identify a tolerable dose of the combination for further studies, to evaluate the anti-tumor activity of the combination, and to investigate candidate predictive biomarkers (ClinicalTrials.gov Identifier: NCT02493751). One regimen was evaluated in the dose-finding phase (a 7-day lead-in period with axitinib 5 mg oral twice daily (BID) followed by avelumab 10 mg/kg intravenously (IV) Q2W in combination with axitinib 5 mg oral BID). The maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) were determined to be avelumab 10 mg/kg IV Q2W with axitinib 5 mg oral BID. In the dose expansion phase, both a 7-day lead in period with axitinib 5 mg oral BID followed by avelumab 10 mg/kg IV Q2W in combination with axitinib 5 mg oral BID (10 patients) and avelumab 10 mg/kg IV Q2W in combination with axitinib 5 mg oral BID (39 patients) were

evaluated. No differences in safety and efficacy were apparent when reviewing the data from the 16 patients who received lead-in axitinib (6 patients in the dose-finding cohort and 10 patients in the dose expansion cohort) and the 39 patients in the dose-expansion cohort who did not receive axitinib lead-in; data from both cohorts were therefore analyzed together.

As of 13 April 2017, per the investigator's assessment of response according to RECIST v.1.1, 32/55 (58.2%) patients had a confirmed objective response (95% CI: 44.1-71.3). A total of 3/55 (5.5%) patients developed a CR, 29/55 (52.7%) patients had a PR, and 11/55 (20%) patients had stable disease (SD) as best overall response (BOR). An objective response of SD or better (disease control) was achieved in 43/55 (78.2%) patients. Response occurred at the time of the first tumor assessment in 20/32 patients and, at the data cut-off date, responses were ongoing in 24/32 patients. The probability of an ongoing response (ie, no disease progression or death) at 12 months was 75.0% (95% CI: 54.3–87.3). A total of 45/54 (83%) patients experienced tumor shrinkage (1 patient died prior to the first oncologic assessment).

The most frequent treatment-related adverse events (TRAEs), ie, those reported for ≥20% of patients, and any Grade 5 TRAEs are shown in Table 1. A total of 32 (58.2%) patients had a TRAE of Grade ≥3 severity: 26 (47.3%) patients had Grade 3 TRAEs, 5 (9.1%) patients had a Grade 4 TRAE, and 1 (1.8%) patient had a Grade 5 TRAE (myocarditis). The autopsy of the patient with a Grade 5 TRAE indicated immune myocarditis.

Table 1. Study B9991002 Treatment-Related (Avelumab- and/or Axitinib-Related) Adverse Events by Preferred Term

	N=55 n (%)			
	All Grades	**Grade 3**	**Grade 4**	**Grade 5**
Any TRAE	53 (96.4)	26 (47.3)	5 (9.1)	1 (1.8)
Diarrhoea	32 (58.2)	2 (3.6)	0	0
Hypertension	26 (47.3)	16 (29.1)	0	0
Dysphonia	26 (47.3)	0	0	0
Fatigue	25 (45.5)	2 (3.6)	0	0
PPE syndrome	17 (30.9)	4 (7.3)	0	0
ALT increased	16 (29.1)	4 (7.3)	0	0
Rash	16 (29.1)	1 (1.8)	0	0
AST increased	14 (25.5)	1 (1.8)	0	0
Hypothyroidism	14 (25.5)	0	0	0
Amylase increased	13 (23.6)	3 (5.5)	1 (1.8)	0
Decreased appetite	13 (23.6)	1 (1.8)	0	0
Mucosal inflammation	13 (23.6)	1 (1.8)	0	0
IRR	11 (20.0)	1 (1.8)	0	0
Lipase increased	11 (20.0)	1 (1.8)	3 (5.5)	0
Nausea	11 (20.0)	1 (1.8)	0	0
Myocarditis	1 (1.8)	0	0	1 (1.8)

Table includes any grade TRAEs observed in ≥20% of patients and Grade 5 TRAEs observed in any patient.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; IRR=infusion-related reaction: N/n=number of patients/number of patients with TRAEs; PPE=palmar-plantar erythrodysesthesia; TRAE=treatment-related adverse event.

A total of 23 (41.8%) patients experienced an immune-related AE (irAE) (Table 2). The most frequent irAE was hypothyroidism (12 [21.8%] patients). Five (5, 9.1%) patients experienced a total of 7 irAEs of Grade ≥3 severity: Grade 3 ALT increased in 2 (3.6%) patients, Grade 3 drug eruption, rash, AST increased, and diarrhoea each in 1 (1.8%) patient, and Grade 5 myocarditis in 1 (1.8%) patient.

Table 2. Study B9991002 Immune Related Adverse Events by Preferred Term

	n (%) N=55			
	All Grades	**Grade 3**	**Grade 4**	**Grade 5**
Any irAE	23 (41.8)	4 (7.3)	0	1 (1.8)
Hypothyroidism	12 (21.8)	0	0	0
Blood TSH increased	1 (1.8)	0	0	0
Hyperthyroidism	3 (5.5)	0	0	0
Pruritus	1 (1.8)	0	0	0
Rash papular	1 (1.8)	0	0	0
Dermatitis acneiform	1 (1.8)	0	0	0
Drug eruption	1 (1.8)	1 (1.8)	0	0
Rash	2 (3.6)	1 (1.8)	0	0
Rash pustular	1 (1.8)	0	0	0
Hepatitis (ALT increased)	3 (5.5)	2 (3.6)	0	0
Hepatitis (AST increased)	2 (3.6)	1 (1.8)	0	0
Diarrhoea	1 (1.8)	1 (1.8)	0	0
Adrenal insufficiency	1 (1.8)	0	0	0
Myocarditis	1 (1.8)	0	0	1 (1.8)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; irAE=immune-related adverse event; N=number of patients; TSH=thyroid stimulating hormone.

In conclusion, for this patient population, the safety profile of the combination was tolerable, manageable, and consistent with the known safety profiles of avelumab[50] and axitinib[57] when administered as monotherapy.

This combination is being evaluated in the Phase 3 study B9991003 (NCT02684006): A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer (JAVELIN Renal 101).

1.2.7. Study Rationale for Tumor Types Under Evaluation

With evolving data it is becoming evident that combination immunotherapy strategies will be necessary to achieve enhanced anti-tumor activity for patients who do not experience disease control with single-agent immune checkpoint inhibitors.[1] Growing nonclinical and clinical evidence suggest that the combination of checkpoint inhibition plus antiangiogenic agents may potentially improve anti-tumor activity and patient outcomes compared to results seen with single agents. VEGF can exert immunosuppressive effects in tumors by inhibiting maturation of dendritic cells, promoting immune suppressive cell infiltration and enhancing immune checkpoint molecule expression.[62] Likewise, immunosuppressive cells such as myeloid derived suppressor cells secrete pro-angiogenic factors VEGF and MMP which directly promote angiogenesis growth[63] and induce resistance to anti-VEGF therapy. Given the immunomodulatory and anti-angiogenic properties of anti-VEGF therapies, including

axitinib,[62-66] potential synergy with anti-VEGF therapy in combination with immune checkpoint blockade may increase clinical efficacy in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

The two tumor types selected for the study are responsive to monotherapy checkpoint inhibition which is available as standard-of-care for these indications. In addition, avelumab has shown preliminary evidence of clinical activity as monotherapy in these tumor types (NSCLC[51] and UC[67]); see Section 1.2.3.2 and Section 1.2.3.3 respectively). Furthermore, NSCLC and UC have demonstrated sensitivity to anti-VEGFR-2 inhibition in combination with chemotherapy.[33,45,47,49] However, despite these therapies, substantial clinical unmet needs exist as the majority of patients experience disease progression during the course of their treatment.

Recently, cabozantinib, a multi-kinase TKI for VEGFR2, mesenchymal-epithelial transition factor (MET) and AXL, in combination with nivolumab ± ipilumumab showed preliminary anti-tumor activity and a manageable safety profile in heavily pretreated, advanced genitourinary (GU) malignancies.[68] ORR for evaluable patients was 33% with a median PFS of 5.9 months (95% CI: 4.5-10.1 months) and median OS of 20 months (95% CI: 10.6 months-undefined). Of the 42 patients treated, 15 patients (13 evaluable) with advanced UC demonstrated an ORR of 38%.[68] Other ongoing anti-VEGF plus immune checkpoint combination trials include ramucirumab plus pembrolizumab which is being evaluated in multiple tumor cohorts including second-line UC and previously treated NSCLC. In the UC cohort, preliminary results for 24 treated patients showed anti-tumor activity with a RR of 8% and SD of 42%; median PFS was 1.87 months (95% CI: 1.28-3.38 months).[69] Among 27 patients in the NSCLC cohort, ORR was 30%, median PFS was 9.7 months (95% CI: 4.6-11.5 months) and the OS rate at 6 months was 84.9%.[70] There were no new safety signals for either cohort.

1.2.8. Summary of Benefit/Risk Assessment

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

The benefit-risk relationship has been carefully considered in the planning of this trial. Avelumab demonstrated clinical activity in patients with advanced solid tumors, including NSCLC (first-line and second-line or higher), breast cancer, CRPC, UC and ovarian cancer CCI CCI [redacted] Infusion-related reactions, including hypersensitivity and irAEs/autoimmune disorders, have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These

include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with an antihistamine and acetaminophen prior to the first 4 avelumab infusions (Cycles 1-2) and as clinically indicated thereafter.

Thus far, avelumab has demonstrated a manageable safety profile and significant anti-tumor activity in various tumor types.[50]

Axitinib is approved multi-nationally for the treatment of advanced RCC after failure of one prior systemic therapy. The adverse events reported for axitinib are well characterized in clinical studies and considered tolerable and manageable (see Section 1.2.4). Furthermore, axitinib demonstrated acceptable toxicity profile as a monotherapy or in combination with other agents.

The combination of avelumab with axitinib is currently being tested in study B9991002, as described in Section 1.2.6. Overall, the safety profile of the combination appears manageable and in line with that of individual agents. One case of fatal myocarditis has occurred in a patient after 19 days of treatment with the combination and 5 days after the second dose of avelumab. CCI [redacted]

Severe or fatal myocarditis has also been reported in literature with pembrolizumab single-agent,[71,72] nivolumab single-agent,[73] nivolumab in combination with ipilimumab,[74] and ipilimumab single-agent,[75] either as single adverse events or in the context of more complex autoimmune syndromes. For ipilimumab, myocarditis (including with fatal outcome) is reported in the prescribing information with a frequency <1%.[76] Guidelines about the management of suspect or confirmed cases of myocarditis and relevant avelumab management instructions have been included in Table 6.

This combination is being evaluated in the Phase 3 Study B9991003 (NCT02684006): A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer (JAVELIN Renal 101).

Based on the manageable safety profiles of avelumab and axitinib and its' enhanced anti-tumor activity in advanced RCC, the anticipated benefit-risk relationship of avelumab given in combination with axitinib is expected to be favorable for investigation in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy, and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

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2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• To evaluate the ORR based on Investigator assessment, per RECIST v1.1 of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.	• Confirmed OR based on Investigator assessment per RECIST v1.1.[77]
Secondary Objectives:	**Secondary Endpoints:**
To evaluate the following in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease: • The safety and tolerability of avelumab in combination with axitinib; • The anti-tumor activity of avelumab in combination with axitinib; • The pharmacokinetics of avelumab and axitinib when administered in combination; • Candidate predictive and/or early response biomarkers in pre-treatment tumor tissue and pre- and post-treatment blood samples that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib. Assessments may include but are not limited to tumor mutational burden, immune repertoire and PD-L1 expression within the tumor microenvironment; • The immunogenicity of avelumab when combined with axitinib.	• AEs as characterized by type, severity as graded by NCI CTCAE v.4.03, (Appendix 2), timing, seriousness, and relationship to study treatments; • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing; • Time-to-event endpoints including TTR, DR, PFS based on Investigator assessment per RECIST v1.1, and OS; • Pharmacokinetic parameters including trough and maximum concentrations (C_{trough}, C_{max}) of avelumab and axitinib; • Tumor tissue biomarker status (ie, positive or negative based on, for example, PD-L1 expression and/or quantitation of tumor mutational burden as well as characterization of the immune repertoire in peripheral blood and/or tumor); • ADA titers and NAb against avelumab.

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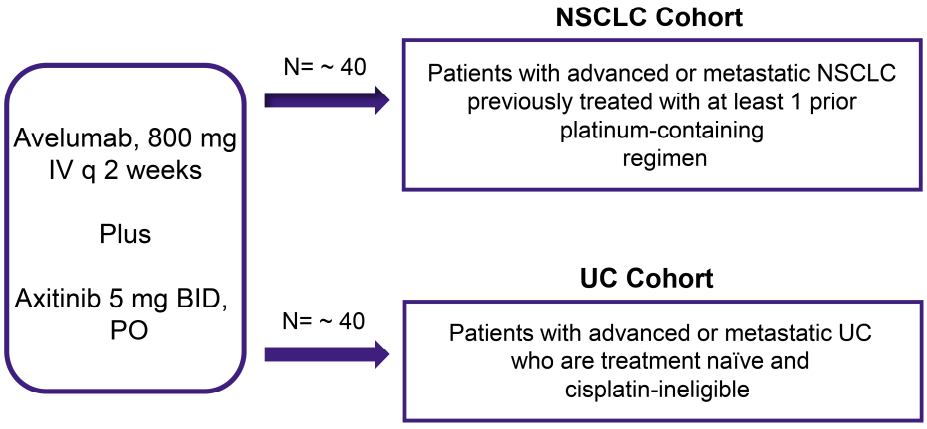
3. STUDY DESIGN

This is an open-label, multi-center, Phase 2 study to evaluate the safety and efficacy of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy, and in patients with advanced or metastatic UC, who are treatment naïve and ineligible for cisplatin-containing chemotherapy for their advanced disease.

Approximately 40 patients will be enrolled in each cohort, NSCLC and UC. See Figure 1.

Figure 1. Study Schema



Patients will receive avelumab 800 mg IV Q2W on Days 1 and 15 of each 28 day cycle in combination with axitinib 5 mg PO BID on a continuous dosing schedule. 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. PATIENT 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.

An eligibility worksheet will be provided to the Investigator and site personnel in order to document the review of inclusion and exclusion criteria for each patient. The eligibility worksheet will be sent to the Sponsor for approval in order to complete enrollment, which defines enrollment into the study, for each patient.

4.1. Inclusion Criteria

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

1. Diagnosis:

    a. NSCLC Cohort: Histologically or cytologically confirmed diagnosis of NSCLC that is locally advanced or metastatic:

    - No activating EGFR mutations, Anaplastic lymphoma kinase (ALK) translocations/rearrangements, or c-ros oncogene 1 (ROS1) translocations/rearrangements where testing is standard of care.
    - Have received at least 1 prior platinum-based chemotherapy regimen for locally advanced or metastatic NSCLC.
    - No more than 2 prior lines of systemic therapy for locally advanced or metastatic disease.
    - If disease progression occurred during or within 6 months after neoadjuvant/adjuvant chemotherapy or radiotherapy-chemotherapy, the regimen is counted as 1 prior treatment regimen towards the allowed limit of prior treatment regimens.
    - Checkpoint inhibitor naïve.

    b. UC Cohort: Histologically or cytologically confirmed diagnosis of transitional cell carcinoma (TCC) of the urothelium (if mixed, more than 50% TCC component) including bladder, urethra, ureters, or renal pelvis that is locally advanced or metastatic:

    - No prior systemic treatment for locally advanced or metastatic disease. Prior neoadjuvant or adjuvant therapy is permitted if disease progression occurred >12 months after the completion of therapy.
    - Checkpoint inhibitor naïve.
    - Ineligible for receiving cisplatin-containing front-line chemotherapy based at least one of the following criteria:[19]

        i. ECOG performance status (PS) 2;

        ii. Renal dysfunction (defined as creatinine-clearance <60 ml/min);

        iii. Grade ≥2 peripheral neuropathy;

iv. Grade ≥2 hearing loss (hearing loss measured by audiometry of 25 decibels at two contiguous frequencies).

2. Measurable disease by RECIST v1.1 with at least 1 measurable lesion that has not previously been irradiated.

3. Availability of an archival formalin-fixed and paraffin-embedded (FFPE) tumor tissue block from primary diagnosis specimen or metastatic specimen (if available). If a FFPE tissue block cannot be provided, then 15 unstained slides (10 minimum) will be acceptable. If such an archived sample is not available, a de novo (ie, fresh) tumor sample must be obtained prior to study enrollment (see Section 6.1.1).

4. ECOG PS: 0 or 1. For UC patients, ECOG PS 2 is permitted as part of cisplatin-ineligibility criteria.

5. Age ≥18 years.

6. Estimated life expectancy of at least 90 days.

7. Adequate hepatic function defined by:

   a. Total serum bilirubin ≤1.5 × the upper limit of normal range (ULN);

   b. AST and ALT ≤2.5 × ULN; for subjects with documented metastatic disease to the liver, AST and ALT levels ≤5 × ULN.

8. Adequate bone marrow function including:

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

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

   c. Hemoglobin ≥9 g/dL (≥5.6 mmol/L) (may have been transfused).

9. Adequate renal function defined by:

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

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

10. Left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN) as assessed by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO).

11. 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.

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

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

14. Female patients of childbearing potential must have negative serum pregnancy or urine pregnancy test at screening. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

    a. 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;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Prior immunotherapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-glucocorticoid induced tumor necrosis factor (TNF) receptor (GITR), anti-lymphocyte activation gene-3 (LAG-3), anti-T cell immunoglobulin and mucin (TIM-3) domain, or anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibody (including ipilimumab).

2. Prior treatment with an anti-VEGF pathway TKI; prior use of anti-VEGF pathway mAb is permitted.

3. Patients with newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to enrollment, have discontinued corticosteroid treatment for these metastases for at least 14 days prior to study enrollment, and are neurologically stable.

4. Diagnosis of any other malignancy within 5 years prior to study enrollment. Adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the bladder, breast, or cervix, or low grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) are allowed.

5. Radiologically documented evidence of major blood vessel invasion or encasement by cancer (ie, invasion into the fat plane between the vessel wall and tumor) or intratumor cavitation, regardless of tumor histology.

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

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

8. Prior organ transplantation including allogenic stem-cell transplantation.

9. Active infection requiring systemic therapy.

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

11. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

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

13. Known prior severe hypersensitivity to the investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥3).

14. Persisting toxicity related to prior therapy (NCI CTCAE v4.03 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. For UC patients, Grade ≥2 peripheral neuropathy is permitted as part of cisplatin-ineligibility criteria.

15. NCI CTCAE Grade ≥3 hemorrhage within 28 days prior to study enrollment.

16. Hemoptysis (≥1/2 teaspoon of bright red blood episode with cough) within 28 days prior to enrollment.

17. Evidence of inadequate wound healing.

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

19. Any of the following in the previous 6 months prior to study enrollment: deep vein thrombosis or symptomatic pulmonary embolism.

20. Any of the following within the 12 months prior to study 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.

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

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

23. Spinal cord compression unless the patient has good pain control attained through therapy, and there is stabilization or recovery of neurological function for the 4 weeks prior to first dose of study drug.

24. Known history of immune-mediated colitis, inflammatory bowel disease, immune-mediated pneumonitis, pulmonary fibrosis.

25. 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 3 months;
    - Active gastrointestinal bleeding, unrelated to cancer, as evidenced by clinically significant hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    - Malabsorption syndromes.

26. Major surgery ≤28 days or major radiation therapy ≤14 days prior to study enrollment. Prior palliative radiotherapy (≤10 fractions) to metastatic lesion(s) is permitted, provided it has been completed at least 48 hours prior to study enrollment. Port placement is considered to be minor surgery.

27. 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 first dose of study drug (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, diltiazem, and conivaptan). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

28. Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers, including their administration within 10 days prior to first dose of study drug (eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St John's wort).

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

30. Participation in other studies involving investigational drug(s) within 28 days prior to study enrollment.

31. Other severe 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. 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.

33. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined in Section 4.3.1) as outlined in this protocol for the duration of the study and for at least 30 days after the last dose of avelumab (90 days for males) and 90 days after the last dose of axitinib.

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 contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and for at least 30 days after the last dose of avelumab (90 days for male patients) and 90 days after the last dose of axitinib. The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected 2 appropriate methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) for the individual patient and his/her partner(s) 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 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 with low user dependency include (applies to female patients at risk for pregnancy with their male partners):

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, inserted, injected, implanted), 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 sterilization with absence of sperm in the postvasectomy ejaculate.

4. 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

At the time that a patient has signed informed consent and entered screening, the site should contact the interactive response technology (IRT) system to obtain the patient identification number.

Once a patient has met all eligibility criteria, assignment of patient enrollment number, patient enrollment, and allocation of investigational product will be managed by the IRT system. The site will need to contact the IRT system to enroll the patient and to obtain the study drug allocation information. At the time of enrollment, site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including, but not limited to, the user's identification and password, the protocol number, and the patient enrollment number. The IRT system will then provide a treatment assignment and dispensable unit (DU) or vial or bottle number for each investigational product to be dispensed. The IRT system will also provide a confirmation report containing the patient number and DU or vial or bottle numbers assigned. The confirmation report must be stored in the site's files.

Study treatment must be initiated preferably on the day of enrollment, but no later than 3 calendar days after enrollment.

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

5.2. Treatment Duration

Patients will continue to receive study treatment until objective disease progression assessed by investigator (see Section 5.5.3 for guidance on treatment beyond progression), patient refusal, unacceptable toxicity, global deterioration of health status requiring discontinuation or until the study is terminated by the Sponsor, whichever occurs first.

5.3. Patient Compliance

5.3.1. IV Administered Investigational Product

For avelumab, the site will complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the Pfizer monitor.

The information related to each trial drug administration, including the date, time, and dose of study drug, will be recorded on the case report form (CRF). The Investigator will ensure that the information entered into the CRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

Non-compliance is defined as a patient missing >1 infusion of any investigational product for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance will have been met as well.

5.3.2. P.O. Administered Investigational Product

For axitinib, patients will be required to return all unused study treatment at the beginning of each cycle. The number of tablets returned by the patient at the end of the cycle will be counted, documented, and recorded for drug accountability. Treatment compliance (reported as a percent) will be defined as the number of tablets taken during the study divided by the expected number of tablets multiplied by 100%. Tablets that are not returned will be considered to have been taken unless reported otherwise by the patient. Drug diary records will be provided to the patients as an aid for the recording of study treatment compliance.

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

5.4. 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.

5.4.1. Dosage Form(s) and Packaging

5.4.1.1. Avelumab

Avelumab is a sterile, clear and colorless to slightly yellow solution intended for IV administration. Avelumab is formulated as a 20 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.

5.4.1.2. 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.

5.4.2. 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.

5.4.2.1. 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 Instructions 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 Instructions 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.

5.4.2.2. Axitinib

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

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

Axitinib will be dispensed on Day 1 of each cycle or as otherwise indicated. Patients should be instructed to keep their study treatment in the bottles provided and not transfer it to any other container. In the event of dose modification, a request should be made of the patient to return all previously dispensed study treatment to the clinic.

5.5. Administration

All investigational products will be administered on an outpatient basis.

5.5.1. 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 Q2W on Days 1 and 15 of each 28 day cycle after all procedures/assessments have been completed as described in the Schedule of Activities table. After Cycle 1, Day 1, avelumab may be administered up to 3 days before or after the scheduled Days 1 and 15 of each dose.

Avelumab will be administered as an 800 mg fixed dose via a 1-hour infusion. Sites should make every effort to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes and +20 minutes is permitted (ie, infusion time is 60 minutes: -10 min/+20 min). The exact duration of infusion should be recorded in both source documents and CRF.

In order to mitigate avelumab infusion-related reactions, patients must 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 IV or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids.

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 4 and Section 5.5.5. Possible modifications of the infusion rate for the management of infusion-related reactions related to avelumab are described in Section 5.5.5.5.

5.5.2. Axitinib

Axitinib will be administered at 5 mg PO BID, with our without food, 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 5.5.5). 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 any time 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 3 and Table 4.

5.5.3. Treatment After Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as avelumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. Following immunotherapy, a clinical response may occur later than would typically be expected following treatment with a cytotoxic agent. In addition, this response may occur after an initial increase in tumor burden or even after 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. Patients may continue to receive avelumab and axitinib at the Investigator's discretion 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.

Before continuation of treatment after initial PD, the patient must be re-consented via informed consent addendum and informed that by continuing to receive the investigational products on study, the patient may be foregoing approved therapy with possible clinical benefit(s).

If repeat imaging does not confirm PD, treatment with avelumab and axitinib may be continued.

If the repeat imaging confirms PD, patients should discontinue from all investigational products. 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 axitinib and avelumab. 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.

If the patient is subsequently found to have further disease progression either radiologically according to RECIST v 1.1 or clinically, then treatment with axitinib and avelumab should be permanently discontinued.

5.5.4. 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]).

5.5.5. 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 4. 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 3.

5.5.5.1. 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 3 (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 3. Axitinib Dose Levels

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

Patients will be monitored closely for toxicity, and axitinib treatment may be adjusted by dosing interruption with or without dose reduction as indicated in Table 4. Dosing interruption and/or dose reduction by 1, and if needed, 2 dose levels (one dose level decrease at a time) as indicated in Table 3 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.

5.5.5.2. Management of Axitinib-Related Hypertension

Patients will be issued BP monitoring devices including 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.[78,79] To treat an increase in BP, standard antihypertensives in accordance to local standard of care may be used except diltiazem (eg, thiazide or thiazide-like diuretics, angiotensin II receptor blockers, angiotensin converting-enzyme inhibitors, and dihydropyridine (DHP) calcium channel blockers, beta blockers, etc.).[78,79]

Dose modification for axitinib in case of hypertension is described in Table 4.

5.5.5.3. 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 4. 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 4. 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		
	<2 g proteinuria/ 24 hour or UPC <2	• Continue at the same dose level.	

Table 4. **Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity (continued)**

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 5.5.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.
	2 systolic BP readings separated by at least hour show systolic pressure >150 mm Hg OR 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 5.5.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 4. **Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity (continued)**

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 5.5.5.2 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 5.5.5.2 for monitoring/management of axitinib-related hypertension.	• Continue as per schedule.

Table 4 **Axitinib Dose Modifications and Avelumab Infusion Omissions for Investigational Product-Related Toxicity (continued)**

Toxicity	NCI CTCAE Severity Grade	Axitinib Dose Modification	Avelumab Treatment Modification
Infusion-related Reaction	Grade 1-4	• Continue at the same dose level.	See Section 5.5.5.5 and Table 5.
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 5.5.5.6 and Table 6.
Stevens-Johnson syndrome	Grade 3-4	• Permanent discontinuation	• Permanent discontinuation
Other Non-hematologic Toxicities and Laboratory Abnormalities	Grade 1	• Continue at the same dose level.	• Continue as per schedule
	Grade 2	• Continue at the same dose level.	• Continue as per schedule
	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.

For NSCLC patients:

Patients with NSCLC who develop symptomatic brain metastases, tumor encasing vasculature, patients on anticoagulants, and patients with hemoptysis or any other relevant risk factors for pulmonary hemorrhage (such as bleeding diathesis) while on study treatment should be discussed with the sponsor and have treatment with axitinib permanently discontinued. However, if brain metastases are successfully treated, or if a patient no longer needs anticoagulation, or bleeding disorder resolves, then treatment could be restarted at the discretion of the investigator and upon discussion with the sponsor.

5.5.5.4. Special Precautions for Avelumab Administration

As with all monoclonal antibody therapies, there is a risk of allergic reactions including anaphylactic shock. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures.

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

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, 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 30 minutes 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 Section 5.5.5.5 and Table 5, 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 5.5.5.6.

5.5.5.5. 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, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of infusion-related reactions should follow the guidelines set forth in Table 5.

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

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50%* and monitor closely for any worsening.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate* once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening. • If a Grade 2 infusion related reaction does not improve or worsens following the decrease in infusion rate and appropriate symptomatic treatment the infusion should not be resumed for that day.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, 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 subject. • Subjects 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 Event; NSAIDs: nonsteroidal anti-inflammatory drugs.

*If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

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

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

5.5.5.6. Management of Avelumab Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity as reported in Table 6:

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring;
- Grade 1 to 2 (persistent): manage similar to 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 6.

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 5.5.5.6.

For overlapping potential immune-related toxicities, follow the specific management recommendations described in Table 6.

Table 6. Management of Avelumab Immune Related Adverse Events

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

Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone 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 for opportunistic infections. Consider bronchoscopy, lung biopsy.	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper. If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy, lung biopsy.	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy.	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.

Grade 2 AST or ALT >3.0 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days.	If returns to Grade ≤1: Resume routine monitoring; resume avelumab therapy. If elevation persists >5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN	Permanently discontinue avelumab therapy. Increase frequency of monitoring to every 1 to 2 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist/ hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily. If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy.	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN	Withhold avelumab therapy. Increase frequency of monitoring to every 3 days. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy.	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.

Grade 4 Creatinine increased >6 x ULN	Permanently discontinue avelumab therapy. Monitor creatinine daily. 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider renal biopsy. Nephrology consult.	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).

*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy. Endocrinology consult if needed. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis).	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy. Consider hospitalization. Endocrinology consult. Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis).	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • 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.	

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

5.6. 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.

5.7. 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 visit and at the end of the trial.

5.8. 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.

5.9. Concomitant Treatment(s)

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period.

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 discretion of the treating physician.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment(s) and up to 90 days after the last dose of study treatment(s). 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, as well as non-drug supportive interventions (eg, transfusions).

Concurrent anti-cancer therapy with agents other than study treatments 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 5.5.5.5 and Section 5.5.5.6, respectively.

5.9.1. Inhibitors and Inducers of Cytochrome P450 (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, diltiazem 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, a dose reduction of approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA dose should be returned (after 3 to 5 half-lives of the inhibitor) to that used prior to initiation of the strong 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.

5.9.2. Hematopoietic Growth Factors

Granulocyte colony stimulating factor may be used in agreement with American Society of Clinical Oncology (ASCO) guidelines[80] or as allowed per local guidance.

Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.9.3. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study.

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).

There is no evidence suggesting that treatment with avelumab increases surgical risk. Postoperatively, the decision to reinitiate investigational products should be discussed with the Sponsor.

In the case that a surgical procedure is required for palliative care, all attempts should be made to rule out disease progression beforehand.

5.9.4. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline; otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression. Study treatment should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion.

5.9.5. Other Prohibited Concomitant Medications and Therapies

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

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than investigational products.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.9.4).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see). See below Clarification Regarding Steroid Use.
- Other experimental pharmaceutical products.
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactivated vaccines (eg, influenza vaccine).
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or those known to potentially interfere with major organ function (eg, hypericin).
- Bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to enrollment.

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

Restrictions for Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[81,82] Furthermore, as for all immunotherapies intended to augment T-cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA-4 compounds indicate that short term use of steroids can be employed without compromising clinical outcomes.[82] Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and for the treatment of irAEs, steroids are permitted according to the modalities indicated in Table 6.

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

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

5.10. Rescue Medications and Supportive Care

5.10.1. 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.[88]

- 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.[89] Patients should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 6.

- Anti-inflammatory or narcotic analgesics may be offered as needed.

- 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

Archived tumor tissue from the most recent primary or metastatic tumor biopsy or resection is required to be available. If there is no archived tumor available, then a *de novo* (ie, fresh) tumor sample should be obtained prior to study enrollment.

For any sample of tumor tissue, one FFPE tissue block should be provided if available and permitted by local laws and policies. If one or more blocks cannot be provided for these reasons, then sections must be freshly cut (ie, cut no more than 30 days prior to shipment to the central laboratory), 4-5 μm thick and mounted on positively-charged microscope slides (SuperFrost Plus glass slides are recommended). Fifteen slides (minimum 10) should be provided.

A minimum 18 gauge core needle should be used in biopsies in order to maximize the quality and value of obtained tissue; a minimum of 3 separate cores is requested for each biopsy procedure. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted.

Additional information on tumor biospecimen collection procedures is included in the Study Manual.

6.2. Study Treatment Period

For treatment period procedures, see the Schedule of Activities.

6.3. Patient Withdrawal/End of Treatment

For End of Treatment visit procedures, please see Schedule of Activities and Section 7.

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

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.5.3 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to 1 of the investigational products, the Investigator may continue treatment with the other investigational product(s);
- Pregnancy;

- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from the study 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 for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

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

6.3.1. 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 (in which case the withdrawal of consent form is not applicable) or also from study procedures and/or posttreatment study follow-up (in which case a withdrawal of consent form should be provided and signed). 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.

6.3.2. 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.

6.4. Short-Term Follow-up

For follow-up procedures see the Schedule of Activities and ASSESSMENTS section.

In Short-term Follow-up, patients should be evaluated up to 90 days (30 days, 60 days, and 90 days ±3 days) after last dose of investigational product(s) for safety or until the time of initiation of new anti-cancer treatment. Patients continuing to experience study drug-related toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks regardless of initiation of new anti-cancer treatment until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Physical examination, ECOG status, vital signs, and safety laboratory measurements are not required for patients who initiate new anti-cancer treatment, unless the patient continues to experience toxicity following discontinuation of the investigational products. Contraception check and serum/urine pregnancy tests are required up to 30 days after last dose of avelumab (90 days for male patients) and 90 days after last dose of axitinib for all patients who enter Short-term Follow-up regardless of initiation of subsequent anti-cancer therapy.

6.5. Long-Term Follow-up

Following completion of the Short-term Follow-up period, all patients will be followed for survival and subsequent anti-cancer treatments every 12 weeks (±14 days) until death, end of the study, or patient withdrawal of consent, whichever comes first; new systemic anti-cancer treatment will also be recorded. These visits may be conducted in-clinic or by remote contact (eg, telephone).

Patients whose disease has not progressed at the time of End of Treatment will continue to undergo disease assessments every 8 weeks for 1 year from the start of study treatment and then every 12 weeks thereafter until documented disease progression regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy (see Section 7.6).

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 fashion.

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 treatments. See also Schedule of Activities.

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, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatments; once at the start of screening and once at the baseline visit, immediately before study drugs administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational products. Additional pregnancy tests (serum or urine) will be repeated at every treatment cycle, on the day of dosing (results should be available prior to dosing), during the active treatment period, at the end of treatment, during follow-up for at least 90 days after the last dose of axitinib or for at least 30 days after last dose of avelumab 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 IRBs/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 should remain in the study. See also Schedule of Activities.

7.1.2. Contraceptive Check

Fertile male patients and female patients who are of childbearing potential, who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined in Section 4.3.1). The Investigator or his or her designee will discuss with the patient the need to use 2 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. 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 contraception (at least one of which is considered to be highly effective with low user dependency as defined in Section 4.3.1) throughout the study for at least 90 days after last dose of axitinib or at least 30 days after the last dose of avelumab (90 days for male patients). See Section 4.3.1 for more details.

7.1.3. Adverse Events

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

7.1.4. Laboratory Safety Assessments

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. Laboratory safety assessments may also be performed when clinically indicated. The required laboratory tests are listed in Table 7.

Laboratory safety assessments must be performed and results reviewed by the treating physician prior to study treatment administration.

Table 7. Required Laboratory Tests

Hematology	Hemoglobin Platelets WBC Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils Percentages allowed only if Absolute not available
Chemistry (*denotes core chemistry panel)	ALT*° AST*° Alkaline Phosphatase*° Sodium* Potassium* Magnesium* Chloride* 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
Urinalysis	Protein, glucose, blood
Pregnancy Tests	For female patients of childbearing potential, serum or urine
Thyroid Function Tests:	TSH, free T4
Coagulation Tests	PT or INR°
Other Tests:	ACTH, HBV, HCV serology

° For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids, and acetaminophen levels.

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

7.1.5. Physical Examinations and Vital Signs

Patients will have a physical examination to include major body systems, supine or sitting blood pressure, pulse rate, body temperature, assessment of ECOG performance status, weight, and height (height will be measured at screening only) at the time points described in the Schedule of Activities. Blood pressure and pulse rate should be taken after the patient has been lying down or sitting quietly for at least 5 minutes.

7.1.6. (12-Lead) Electrocardiogram Measurements

A standard 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

A single ECG is to be performed at Screening, as clinically indicated and EOT. Clinically significant abnormal findings in baseline ECGs will be recorded as medical history. If the QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then a triplicate ECG (3 consecutive 12-lead ECGs approximately 2 minutes apart) will be collected to confirm the original measurement. If the mean QTc of the triplicate ECG is >500 msec then the ECGs will be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, single ECGs should be repeated hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring as clinically indicated. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to ≤500 msec. If the QTc interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study.

Each episode of prolongation of the QTc interval will be evaluated by a specialist to determine if due to the investigational product or due to other potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance).

If a patient experiences any cardiac or neurologic AEs (especially syncope, dizziness, seizures, or stroke), an ECG in triplicate should be obtained at the time of the event.

7.1.7. 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. Please see Schedule of Activities.

7.2. Pharmacokinetics Assessments

7.2.1. Blood Sample Collection for Pharmacokinetic Analysis

Blood samples will be collected for PK analysis of avelumab and axitinib into the appropriate tubes as outlined in the Schedule of Activities, Section 7.2.2 and Section 7.2.3. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, with the exception of samples where nominal time coincides with end of infusion, samples obtained within ±10% of the nominal time (eg, within 3 minutes of a 30 minute sample) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). For samples where nominal time coincides with end of infusion, a sample collected within 10 min post end of infusion will not be captured as a protocol deviation. If the infusion of avelumab is interrupted due to AE, any PK samples scheduled during the time of the dosing interruption are not required. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

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7.2.2. Collection of Axitinib Pharmacokinetic Samples

At each time point for axitinib, a 3 mL whole blood sample will be collected into an appropriately labeled K_3EDTA (tripotassium edetic acid [ethylenediaminetetraacetic acid]) 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 sample will be collected into a Serum Separator Tube (SST) at the designated times to provide serum for avelumab PK analysis. Pre-dose samples can be taken up to 2 hours prior to the start of avelumab infusion.

7.3. Immunogenicity Assessment

Blood samples (3.5 mL whole blood) will be collected for assessment of avelumab ADAs into an appropriately labeled SST. Predose ADA samples will be collected within 2 hours prior to dosing. Further details can be found in the Lab Manual. This assessment will take place at regular intervals during the treatment and follow-up periods as described in the Schedule of Activities.

A tiered ADA testing strategy will be used: all samples that are positive in the screening assay will be confirmed for antibody specificity. Confirmed positive samples will be further characterized for titer and tested in the NAb assay, if appropriate.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the trial.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

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7.4. Translational and Pharmacodynamic Assessments

Whole blood samples CCI [redacted] one 10 mL, red-top serum Becton Dickinson (BD) Vacutainer® tube for serum preparation) will be collected at the designated times for secondary CCI [redacted] assessments which may include immune repertoire analysis, and/or epigenetic or proteomic profiles, unless prohibited by local regulation or by decision of the IRB or EC. CCI [redacted]

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[redacted]

Unless prohibited by local regulations or ethics committee decision, a saliva sample will be collected on Cycle 1, Day 1 before the first dose of study drug treatment to be used as a germline control to assist in identifying and profiling tumor mutations.

7.4.1. Archived Tumor Biospecimens and *De Novo* Tumor Biopsies

Archived tumor tissue samples and *de novo* biopsies of primary and/or metastatic lesions (see Section 6.1.1) will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Markers that may be analyzed include, but may not necessarily be limited to, the presence/absence of tumor-infiltrating CD8+ T lymphocytes and/or expression of PD-L1, within the tumor microenvironment and tumor mutational burden.

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[redacted]

7.6. Tumor Assessments

The decision for body areas to be scanned will depend on the disease under study and the extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned depending upon malignancy are detailed in the Imaging Manual.

Baseline scans must be performed within 28 days prior to first dose of study drug.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline, then every 8 weeks from first dose of study drug for 1 year from start of study treatment, and then every 12 weeks thereafter until PD regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities. In addition, radiological tumor assessments will be conducted whenever PD is suspected (eg, symptomatic deterioration).

The schedule of tumor assessments should be fixed according to the calendar regardless of treatment schedule or treatment delays or interruptions due to toxicity.

Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans.

Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom brain metastasis is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post- baseline only when clinically indicated.

Bone imaging using bone scan (bone scintigraphy) (preferred method) or other methods considered standard of care locally such as 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET/CT) or CT or MRI is required at baseline. Bone lesion(s) identified at baseline by bone scan will be further assessed by diagnostic CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by diagnostic CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone scans will only be repeated during study as clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases), at the time of confirmation of CR, and at every other tumor assessment visit (ie, every 16 weeks during the first 12 months of study treatment and every 32 weeks thereafter) if considered local standard of care.

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.

Assessment of response will be made using RECIST v1.1 (Appendix 4) CCI [redacted] 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.

In case CR or PR is observed, tumor assessments must be confirmed on repeated imaging at least 4 weeks after initial documentation. If radiologic imaging shows PD, then the tumor assessment should be repeated after at least 4 weeks to confirm PD. See Section 5.5.3 for treatment after initial evidence of PD. If the patient begins a new anti-cancer therapy prior to confirmation of PD, then the confirmatory assessment is not required.

All patients' files and radiologic images must be available for source verification and for potential peer review. All radiographic images will be collected and stored by an independent third-party imaging laboratory, according to instructions in the Imaging Manual.

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 the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

If a patient begins a new anti-cancer 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 anti-cancer 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.

Death must be reported if it occurs during the SAE reporting period after the last dose of study drug, irrespective of any intervening treatment.

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, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated 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 liver function test (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 exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after 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 a 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 will be documented in a statistical analysis plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

This section describes the data analysis and statistical methods for the combination of avelumab and axitinib.

9.1. Analysis Sets

9.1.1. Full Analysis Set

The full analysis set includes all patients who receive at least 1 dose of study treatment.

9.1.2. Safety Analysis Set

The safety analysis set includes all patients who receive at least 1 dose of study treatment. In this non-randomized study, the full analysis set and the safety analysis set are identical.

9.1.3. Pharmacokinetics Analysis Set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration above the lower limit of quantitation (LLQ) for avelumab or axitinib.

The PK parameter analysis set is a subset of the safety analysis set and will include treated patients who have at least one of the PK parameters of interest for avelumab or axitinib.

9.1.4. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose ADA/NAb sample collected for avelumab.

9.1.5. Biomarker Analysis Set

The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one baseline biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.2. Sample Size Determination

The primary objective is to assess the ORR of avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who have received at least one prior platinum-containing therapy and in treatment naïve patients with advanced or metastatic UC, who are ineligible for cisplatin-containing chemotherapy for their advanced disease.

Approximately 40 patients will be enrolled from each of 2 tumor type cohorts: NSCLC, and UC. Thus, a total of approximately 80 patients will be enrolled.

With 40 treated patients per tumor type cohort, ORR can be estimated with a maximum standard error of 0.079. Assuming a beta (0.5, 0.5) prior,

- NSCLC cohort: if 15 responders (out of 40 patients, ORR of 37.5%) are observed, the probability of a true ORR ≥30% (considered a clinically relevant effect above single-agent checkpoint inhibition,[39-43] [Section 1.2.2]) will be ≥80% (85.0%).

- UC cohort: if 19 responders (out of 40 patients, ORR of 47.5%) are observed, the probability of a true response rate ≥40% (considered a clinically relevant effect above single-agent checkpoint inhibition[25,26] [Section 1.2.1]) will be ≥80% (83.4%).

Table 8 provides the exact 95% confidence intervals for ORR based on different observed number of responders in a given tumor type cohort.

Table 8. Sample Size and Exact 95% CI for ORR

Number of Patients	Number of Responders	Observed ORR	Exact 95% CI for ORR
40	4	10.0%	(2.8% - 23.7%)
	6	15.0%	(5.7% - 29.8%)
	8	20.0%	(9.1% - 35.6%)
	10	25.0%	(12.7% - 41.2%)
	12	30.0%	(16.6% - 46.5%)
	14	35.0%	(20.6% - 51.7%)
	16	40.0%	(24.9% - 56.7%)
	18	45.0%	(29.3% - 61.5%)
	20	50.0%	(33.8% - 66.2%)
	24	60.0%	(43.3% - 75.1%)
	28	70.0%	(53.5% - 83.4%)

CI=confidence interval; ORR=objective response rate.

9.3. Efficacy Analysis

All efficacy analyses will be performed based on the full analysis set for each tumor type cohort separately.

9.3.1. Analysis of the Primary Endpoint

The primary endpoint is confirmed OR based on Investigator assessment per RECIST v1.1.

OR is defined as a CR or PR per RECIST v 1.1 from the first dose of study treatment until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of patients with a confirmed CR or confirmed PR based on Investigator's assessment per RECIST v 1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of ORR. The two-sided exact 95% CIs for ORR will be calculated.

9.3.2. Analysis of the Secondary Efficacy Endpoints

PFS is defined as the time from first dose of study treatment (ie, start date) to the date of disease progression by RECIST v 1.1 or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have any adequate post-baseline tumor assessments will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

TTR is defined for patients with confirmed objective response (CR or PR) as the time from the first dose of study treatment to the first documentation of objective tumor response.

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

OS is defined as the time from the first dose of study treatment to the date of death. Patients without an event (death) will be censored at the date of last contact.

TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods. Point estimates will be presented with 95% CIs. In addition, progression date, death date, date of first response, and last tumor assessment date will be listed, along with BOR, TTR, DR, PFS and OS.

9.4. Analysis of Pharmacokinetics and Pharmacodynamics

9.4.1. Analysis of Pharmacokinetics of Investigational Products

PK data analyses will include descriptive summary statistics (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) of the pre-dose trough (C_{trough}) and post-dose (C_{max}) concentrations for each investigational product by cycle, day and by dose level.

Other PK parameters may be determined if deemed appropriate. The summary data may be compared with the historical data of avelumab and axitinib as single agents to assess the effect of avelumab on the PK of axitinib and the effect of axitinib on the PK of avelumab. The analysis and population modeling analysis report (PMAR), if performed, will be outlined in the statistical analysis plan (SAP).

The trough concentrations for avelumab and axitinib will be plotted versus time for each dose using a box whisker plot by cycle and day in order to assess the attainment of steady state.

9.4.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/Pharmacodynamic) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab and axitinib exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

9.4.3. Analysis of Immunogenicity Data of Avelumab

ADA and NAb data will be listed and summarized for each dosing interval for avelumab. The percentage of patients with positive ADA and NAb will each be summarized by cohort and for all cohorts combined. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab concentrations and pharmacokinetics will be evaluated, if data permit.

9.5. Analyses for Secondary CCI Biomarker Endpoints

For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, percent of coefficient of variation, and minimum/maximum levels) will be determined at baseline and on-treatment/end of treatment time points, as appropriate. Appropriate change from baseline measurements will be provided.

For discrete measurement biomarkers (eg, tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/end of treatment time points. Shift tables may also be provided.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Fisher's exact test, Wilcoxon rank-sum test, Kaplan-Meier estimates, and linear regression as appropriate. The statistical approaches will explore the correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy, such as tumor response and progression free survival.

9.6. Safety Analysis

9.6.1. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on Treatment Emergent Adverse Events, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades.

9.6.2. Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE version 4.03 severity grade whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test.

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

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

9.6.3. Electrocardiogram

Baseline ECG measurements will be summarized by tumor type cohort. Interval measurements from clinically indicated on-treatment ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

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

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval.

9.7. Analysis of Other Endpoints

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

9.8. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label, non-randomized study, the Sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of efficacy and safety assessment, facilitating PK/Pharmacodynamic modeling, and/or to support clinical development.

9.9. Data Monitoring Committee

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

- Surveillance for SAEs according to regulatory guidelines;
- Discussions between the investigators and the sponsor of AEs and laboratory tests alterations seen at each dose level will be performed in an ongoing manner at regular teleconferences and/or meetings to determine the safety profile and risk/benefit ratio and decide if further enrollment is appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and

investigator will promptly resolve any discrepancies that are identified between the study data and the patient's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs 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 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 a Member State

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

13.2. End of Trial in All Other Participating Countries

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

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 one 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.

From: Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.

Appendix 2. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

http://ctep.cancer.gov

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

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

Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

Appendix 4. Response Evaluation Criteria in Solid Tumors Version 1.1

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

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

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

Normal sites

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

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

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

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

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

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

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

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

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

- Indeterminate. Progression has not been documented, and

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

    or

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

    or

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

    or

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

Non-target disease

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

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

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

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

New Lesions

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

Supplemental Investigations

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

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

Objective/Subjective Progression

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

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in table Table 9.

Table 9. Objective Response Status at each Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate or Missing	No	SD
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

Determination of Best Overall Response

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

CCI

[redacted]

CCI

[redacted]

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
ADL	activities of daily living
AE	adverse event
AHFS	American Hospital Formulary Service
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASHP	American Society of Hospital Pharmacists
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
CCI	[redacted]
BD	Becton Dickinson
BID	twice daily
BNP	B-type natriuretic peptide
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CG	Cockcroft-Gault
CI	confidence interval
CK	creatine kinase
CPK	creatinine phosphokinase
CR	complete response
CRF	case report form
CRP	C-reactive protein
CRPC	castration resistant prostate cancer
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CT SAE	Clinical Trial Serious Adverse Event
CV	coefficient of variation
CYP	Cytochrome P450
DHP	dihydropyridine

Abbreviation	Term
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
DU	Dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ESMO	European Society for Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FDG-PET	fluorodeoxyglucose positron emission tomography
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
FFPE	formalin-fixed and paraffin-embedded
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GH	growth hormone
GITR	glucocorticoid induced tumor necrosis factor receptor
GMP	Good Manufacturing Practice
GVHD	graft versus host disease
GU	genitourinary
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HDPE	high-density polyethylene
HR	hazard ratio
IB	Investigator brochure
ICH	International Conference on Harmonisation
ID	identification
IERC	Independent Endpoint Review Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
ir	immune related
irAE	immune-related adverse event

Abbreviation	Term
CCI	[redacted]
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
JM	juxta membrane
CCI	[redacted]
K_3EDTA	tripotassium ethylenediaminetetraacetic acid
LAG-3	lymphocyte activation gene-3
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LSLV	last subject last visit
LLN	lower limit of normal
LLQ	lower limit of quantitation
LSLV	last patient last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCC	Merkel Cell Carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition factor
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	multigated acquisition
N/A	not applicable
NAb	Neutralizing Antibody
NCI	National Cancer Institute
NR	Not reached
NSAIDs	nonsteroidal anti-inflammatory drugs
NSCLC	Non-Small Cell Lung Cancer
OR	objective response
ORR	objective response rate

Abbreviation	Term
OS	overall survival
PCD	primary completion date
PD	progressive disease
PFS	progression free survival
PD-1	Programmed Death-1
PDGFR	Platelet-Derived Growth Factor Receptor
PD-L1	Programmed Death-Ligand 1
PI	principal investigator
PK	pharmacokinetic
PMAR	population modeling analysis report
PO	per Os (by mouth)
PR	partial response
PS	Performance status
PT	prothrombin time
PTs	preferred terms
Q2W	every 2 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumor
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
RR	Response rate
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOA	schedule of activities
SRSD	single reference safety document
SST	serum separator tube
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TCC	Transitional cell carcinoma
TEAE	treatment emergent adverse event
TIM-3	T cell immunoglobulin and mucin domain
TKI	tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TO	Target occupancy
TRAE	Treatment related adverse events
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
UC	urothelial cancer
ULN	upper limit of normal

Abbreviation	Term
US	United States
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VTE	vascular thrombotic events
WBC	white blood cell
WHO	World Health Organization