CLINICAL PROTOCOL

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A PHASE 3, MULTICENTER, MULTINATIONAL, RANDOMIZED, OPEN-LABEL, PARALLEL-ARM STUDY OF AVELUMAB (MSB0010718C) PLUS BEST SUPPORTIVE CARE VERSUS BEST SUPPORTIVE CARE ALONE AS A MAINTENANCE TREATMENT IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC UROTHELIAL CANCER WHOSE DISEASE DID NOT PROGRESS AFTER COMPLETION OF FIRST-LINE PLATINUM-CONTAINING CHEMOTHERAPY

Compound:	MSB0010718C
Compound Name:	Avelumab
United States (US) Investigational New Drug (IND) Number:	126,217
European Clinical Trials Database (EudraCT) Number:	2015-003262-86
Protocol Number:	B9991001
Phase:	3

Document History

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Amendment 6	08 March 2021	As the primary objective for the study was met at the pre-specified interim analysis (Section 9.6), the frequency of study procedures will be reduced while providing continued treatment for patients actively receiving avelumab and study participation will be ended for all patients not actively receiving avelumab (ie, Arm A patients in long-term follow-up and all Arm B patients who have not crossed over to receive avelumab). These changes will be implemented following a final overall survival (OS) update conducted after the target number of OS events has been reached (see Section 9.1). Key changes implemented by Amendment 6 include: • A new Schedule of Activities (SoA) table and a new Required Laboratory Tests table (Table 7) were added. • Blinded independent central review (BICR) tumor assessments will no longer be performed. • Arm B patients who are eligible to crossover to avelumab plus best supportive care (BSC) as per Supplement 1 will be permitted to do so until 60 days after the final OS update or approval of Amendment 6, whichever is later. • CRF data collection will be reduced to those items relating to study drug exposure and adverse events. The following sections were modified based on the above: • Protocol Summary (Study Design, Study Treatment)

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		• 1.2.3.3 Rationale for Study Design • 3.1 Study Overview • 3.1.1 Study Treatment • 3.1.2 Tumor Assessments • 5.4.1 Treatment after Initial Evidence of Radiologic Disease Progression • 5.9 Concomitant Treatments • 6.2 Treatment Period • 6.3 End of Treatment/Withdrawal and Follow-up Visits • 6.5 Patient Withdrawal • 7.1.1 Pregnancy Testing • 7.1.3 Laboratory Safety Assessments • 7.1.4 Physical Examinations and Vital Signs • 7.1.5 (12-Lead) Electrocardiograms • 7.2 Patient-Reported Outcome Assessments • 7.3 Pharmacokinetics Assessments • 7.4 Immunogenicity Assessment • 7.5.2 Peripheral Blood • 7.7 Tumor Assessments • 7.8 Expedited Blinded Independent Central Review for Disease Progression • 9.7 External Data Monitoring Committee

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		• Section 17 SUPPLEMENT 1: Crossover from BSC ALONE (ARM B) to Avelumab plus Best Supportive Care. Additional changes: • For consistency with changes implemented by Protocol Amendment 3, the following sentence was removed from Footnote #3 of the Prior to Protocol Amendment 6: Schedule of Activities for End of Treatment/Withdrawal and Follow-up Periods: "During the post-treatment safety follow-up (beyond 30 days through 90 calendar days after last study administration), AEs (serious or non-serious) that the investigator believes have at least a reasonable possibility of being related to study drug are to be recorded on the case report form (CRF)." • As per Protocol Administrative Change Letter dated 02 Jul 2020, footnote #6 of the Prior to Protocol Amendment 6: Schedule of Activities for Screening and Study Treatment Periods, footnote #5 of the Schedule of Activities for patients who Crossover from Arm B to Avelumab Plus BSC (Supplement 1) and Section 7.1.4 Physical Examinations and Vital Signs were updated to clarify that vital signs should be taken before study drug dosing. • 8.14.2 Non-Serious Adverse Event Reporting Requirements was updated to include an administrative change implemented through a country specific (Japan) Protocol Administrative Change Letter dated 02 July 2020. • As per country specific (Japan) Protocol Administrative Change Letter dated 02 July 2020: Section 12.2 Ethical Conduct

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		of the Study was updated to clarify that after approval of avelumab for advanced urothelial carcinoma by the Japanese Ministry of Health, Labor and Welfare (MHLW), this study will be conducted according to Good Post-Marketing Surveillance Practices (GPSP) in addition to Good Clinical Practice (GCP). • As per the Protocol Administrative Change Letters dated 03 Apr 2020 and 15 Apr 2020, and updated according to the current protocol appendix template for public health emergencies: Appendix 6 Alternative Measures During Public Emergencies was added in response to the ongoing global pandemic COVID-19, and the increasing restrictions on travel, investigational site access issues and concerns on public health in order to clarify alternative solutions that will accommodate study procedures during the COVID-19 pandemic. • Per current best practice, copies of quality of life (QOL) questionnaires (formerly Appendix 5 and Appendix 6) were removed. • Additional minor edits were made throughout the document for clarity and consistency.
Amendment 5	13 February 2020	At the pre-specified interim analysis (Section 9.6), this study met the primary objective and demonstrated that avelumab plus BSC significantly prolongs OS compared to BSC alone in both co-primary populations (ie, in all randomized patients and in patients with PD-L1-positive tumors). Based on this result, the External-Data Monitoring Committee (E-DMC) recommended that remaining patients on

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		Arm B who are progression-free be offered crossover to avelumab. The purpose of this protocol amendment is to implement the E-DMC recommendation. 1. The following sections were modified based on the above: • Protocol Summary (Study Design); • 1.2.3.3 Rationale for Study Design; • 1.3 Summary of Benefit Risk Assessment; • 3.1 Study Overview; • 5.1 Allocation to Treatment. 2. Added Section 17, Supplement 1: Crossover from BSC alone (Arm B) to Avelumab Plus Best Supportive Care. This supplement provides details for Arm B patients who crossover to receive avelumab plus BSC including required eligibility criteria, general treatment/study plan, and schedule of activities for screening, treatment period, end of treatment/withdrawal and short and long-term follow-up.
Amendment 4	28 March 2019	1. Given the lack of standardization, immune-related Response Criteria (irRECIST) has been removed as an exploratory endpoint and required study assessment. Associated elements were revised or removed accordingly in Section 3.1.2 and throughout the document as appropriate. This includes: • The requirement for repeat tumor assessment to confirm progressive disease (PD) was removed.

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		(Section 7.7 and throughout the document as appropriate). • Treatment after PD section was updated as a result of removing the requirement to confirm PD. (Section 5.4.1). 2. Management of avelumab-related toxicity has been updated to reflect current avelumab program standard recommendations (Section 5.4.3). This includes: • Specific recommendations for avelumab-related toxicity provided in Tables 3, 4 and 5 were updated. • Text in the management of avelumab immune-related adverse events and hypersensitivity reactions sections were removed, as the information provided is now covered in other sections. • A 2-hour post-dose observation period is no longer required. • Premedications to mitigate avelumab infusion-related reactions were revised such that premedication is only required for the first 4 infusions. (Section 5.4.3.1. and throughout the document as appropriate). • The avelumab infusion rate may be returned to the baseline rate following a previous reduction due to an infusion-related reaction (Table 4). 3. Contraception requirements have been updated for females and males in accordance with the current Pfizer and avelumab program standards.

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		(Section 4.3.1 and throughout the document as appropriate). 4. The contraception check and pregnancy test were removed as required study procedures at the 60 Day Follow-up visit, in accordance with the current avelumab program standard. (Section 7.1.1 and throughout the document as appropriate). 5. It has been added that if new cancer therapy is started, reporting of concomitant medications should end at the time the new cancer therapy starts in order to match the AE reporting period, and in accordance with the current avelumab program standard. (Section 5.9 and throughout the document as appropriate). 6. The section for rational for immunotherapy treatments in maintenance of UC was updated to include recently published results from a pooled analysis of study EMR 100070-001. (Section 1.2.3.2). 7. Survival assessments for long-term follow-up (every 3 months) were clarified to begin after the last study clinic visit, and to allow additional timepoints at Sponsor request in preparation for interim and final analyses in order to update survival information and add uniformity in the time since most recent contact. (Footnotes in SOA table). 8. Clarifications have been made as follows: • The frequency of bone imaging requirements was clarified to be every 16 weeks for the first year after randomization and every 24 weeks thereafter (ie, at every other tumor assessment). (Section 7.7 and

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		throughout the document as appropriate). • Text was added to clarify that intranasal, inhaled, and topical steroids; local steroid injections; and all inactive vaccines are permitted. (Section 5.9.3 and throughout the document as appropriate). • The list of required lab tests was updated to clarify that glucose testing can be done in a fasted or non-fasted status. (Section 7.1.3). • Clarification was added that the archival tumor tissue sample is not mandatory, in consistency with other sections of the protocol. (SOA table and throughout the document as appropriate). • A window of ±3 days was specified for the radiological tumor assessments to provide clarity for scheduling purposes. (Footnotes in SOA tables). • The reporting of AEs and recording of concomitant medications was clarified for Arm B to end 90 days after the End of Treatment (EOT) visit, instead of 90 days after the last dose of study drug. (SOA tables and throughout the document as appropriate). 9. Additional minor edits were made throughout the document for clarity and consistency.
Amendment 3	19 December 2016	1. Removed a footnote stating "avelumab is the proposed International Nonproprietary Name (INN)…" as this

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		has been endorsed by the governing authorities (Cover Page, Protocol Summary, and Section 1.1). 2. Following the accelerated approval of atezolizumab by the United States FDA, a sentence stating "there are no second-line therapies approved in the United States" was deleted (Protocol Summary and Section 1.2.3.1). 3. To mitigate the potential for bias in determining disease progression, an expedited blinded independent central review (BICR) for investigator-assessed disease progression was added (Section 7.8 and throughout text as appropriate). 4. For patient convenience and to optimize trial logistics, revised text to allow patients to provide informed consent during or after first-line chemotherapy (Protocol Summary, Schedule of Activities for Screening footnote 2, and Section 3.1). 5. To optimize trial logistics, removed the requirement for central eligibility review of first-line chemotherapy response (Protocol Summary; Schedule of Activities for Screening footnotes 16 and 21; Section 3.1; Section 4.1 inclusion criterion 3.a; and Section 7.7). 6. Clarified that the 'FACT Bladder Symptom Index (FBlSI)' is the 'NCCN-FACT FBlSI-18'. This change is indicated in Section 3.1.4 and throughout text where appropriate. 7. For patient/investigator convenience, added a note allowing that laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review (Schedule of

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		Activities for Study Treatment Period footnote 1 and Follow-up Period footnote 1). 8. Per United States FDA request, to assess the utility of serum troponin measurements in early detection of myocarditis, a rare and potentially fatal risk associated with avelumab and other check-point inhibitors, the following additions were made to both study arms: • Mandatory measurement of cardiac troponin levels at screening and at each clinic visit ending on Cycle 4 Day 1 (ie, for a total of 12 weeks), and as clinically indicated (Schedule of Assessments for Study Treatment footnote 12, and Table 6). • Management guidelines for myocarditis (Table 5). • Further information and rationale for this addition in Section 1.2.2.1. 9. To adequately monitor for disease progression, clarified that chest, abdomen, and pelvic CT or MRI scans are required at each tumor assessment time point and for all patients (Schedule of Activities for Study Treatment Period footnote 16 and Follow-up Period footnote 13; and Sections 3.1.2 and 7.7). 10. Revised the requirement for a screening bone scan (or ^{18}FDG-PET scan) to allow alternate modalities (eg, MRI) per local standard of care, as ^{18}FDG-PET scan is not a permissible alternate for bone imaging at some centers and MRI in some countries is the preferred method for bone imaging instead of bone scans (Schedule of Activities for Study Treatment Period footnote 16 and

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		Follow-up Period footnote 13; and Sections 3.1.2 and 7.7). 11. As asymptomatic brain metastases are infrequent in the study population, the requirement for a screening brain scan was changed to apply only to patients with a history of brain metastases or for whom brain metastases are suspected (Schedule of Activities for Study Treatment Period footnote 16 and Follow-up Period footnote 13; and Sections 3.1.2 and 7.7). 12. Per the current standard for the avelumab program, extended the adverse event (AE) collection period for all AEs regardless of causality to 90 calendar days (rather than 30 days) after the last administration of study drug (Schedule of Activities for Study Treatment Period footnote 17 and Follow-up Period footnote 14; and Section 8.2). 13. Clarified and modified requirements relating to the collection of tumor tissue biospecimens (Schedule of Activities for Study Treatment Period footnotes 24 and 25; Schedule of Activities for Follow-up Period footnote 19; inclusion criterion 4; and Section 6.1.1). • Permitted the submission of freshly cut slides in place of tissue blocks for the recent tumor tissue sample and the End of Treatment biopsy, as some investigative centers are not able to submit tissue blocks due to local policy or regulations. • To facilitate patient enrollment, allowed that the recent tumor tissue sample may have been obtained

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		within 24 months prior to randomization (instead of 1 year). • Added that tumor tissue samples obtained from bone metastases are not acceptable, as the processing required for these samples (decalcification) is not compatible with planned analyses. • Clarified the time point for the archival tumor tissue sample collected at the time of the primary diagnosis or first tumor resection (if different from the most recent tumor tissue sample), and removed the availability of this sample as an eligibility requirement to facilitate patient enrollment. 14. Removed ECOG performance status as a survival follow-up procedure as this data is not required for survival analyses and is difficult to reliably collect during long-term follow-up (Schedule of Activities for Follow-up Period footnote 3). 15. Clarified and modified eligibility criteria (Section 4.1 and Section 4.2) to ensure protocol compliance and facilitate patient enrollment: • Clarified eligible tumor stage listed in inclusion criterion 1b and added reference to TNM tumor classification (Section 16). • Clarified that first-line chemotherapy must have been completed no less than 4 weeks and no more than 10 weeks prior to randomization (inclusion criterion 2a).

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		• Revised inclusion criterion 4 relating to tumor sample requirements (as described above). • Revised inclusion criterion 11 to allow alternate methods for estimating creatinine clearance. • Added a higher eligibility limit for AST and ALT elevations in patients with liver metastases consistent with updated inclusion criteria across avelumab program. • Clarified exclusion criterion 2 as being applicable to systemic treatments. • Added exceptions for persisting toxicity related to prior therapy to exclusion criterion 6. • Added exception for patients with resected prostate cancer to exclusion criterion 7. • Revised exclusion criterion 10 relating to prior cardiovascular disease to facilitate patient enrollment and to match the current standard template for avelumab protocols. • Revised exclusion criterion 17 relating to hepatitis B or C for clarity and to match the current standard template for avelumab protocols. 16. Removed a 120 minute maximum limit on the total duration of avelumab infusions as this limit is unnecessary (Protocol Summary, Section 3.1.1, Section 5.4.3.2, and Table 4).

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		17. Removed requirement for testing urine albumin levels (Table 6) as this is not standardly available (eg, in routinely used urine test strips) and is not required as a safety assessment. 18. Removed measurement of avelumab metabolite(s) as this is not a planned pharmacokinetic analysis (Section 7.3). 19. Modified analysis of disease control (Section 9.3.2) as follows: • Added non-CR/non-PD as a response category since patients without measurable disease per RECIST v1.1 are eligible for study participation. • Noted that CR and PR must be confirmed by a repeat assessment, and that the criterion for SD must have been met at least 6 weeks after the date of randomization. • Removed an analysis of the disease control rate at 24 weeks as this is best assessed based on Kaplan-Meier methodology for estimation of progression-free survival rates. 20. In Appendix 3, revised "index" lesions to be "target" lesions for consistency. 21. In Appendix 8, added abbreviations for EuroQol 5 dimension 5 level questionnaire (EQ-5D-5L) and cardiac troponin, and corrected the abbreviation for single reference safety document (SRSD). 22. Minor edits for clarity were made where appropriate throughout text.
Amendment 2	24 March 2016	Per Voluntary Harmonisation Procedure Clinical Trial Application assessment:

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		1. Added an HIV screening test unless not permitted by local laws and regulations (Schedule of Activities table and footnote #12; and Table 6, Section 7.1.3) and exclusion of HIV positive patients (exclusion criterion #16, Section 4.2). 2. Clarified that exclusion criterion #21 (Section 4.2) includes but is not limited to those medical conditions listed, and add 'pulmonary fibrosis' as a listed condition. 3. Clarified in Section 7.1.3 that the requirement to repeat abnormal laboratory test results applies only for clinically significant abnormal results. 4. Clarified in Section 9.6 the stopping rules for efficacy and futility.
Amendment 1	17 December 2015	1. Per FDA request, implemented clarifications in Section 5.4.3.5, Table 5 Management of Avelumab Immune-Related Adverse Events (irAEs): • Clarified requirement for delaying or discontinuing avelumab for Grade 3 or 4 dermatological irAEs. • Clarified requirement to delay or discontinue avelumab therapy for suspicion of adrenal crisis. 2. Per FDA request, added a requirement in Section 5.4.3.5, Table 5, to permanently discontinue avelumab therapy for patients with AST/ALT >3 x ULN with concurrent elevation of total bilirubin >2 x ULN without another obvious cause. 3. Revised Table 3 (Section 5.4.3) to remove redundant items. 4. Section 4.1, inclusion criterion #11 was revised to allow enrollment of patients with a creatinine clearance (CrCl)

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		≥30 mL/min (changed from ≥50 mL/min). • Patients with a CrCl of <60 mL/min are considered to be candidates for first-line gemcitabine+carboplatin chemotherapy. A proportion of these patients would be commonly excluded by a ≥50 mL/min CrCl requirement. Also, patients who initially have a value of >50 could drop to below 50 after completion of platinum based first-line treatment. This lower (but still ≥30 mL/min) permissible inclusion value is anticipated to be safe based on the low incidence of renal toxicity observed in the avelumab studies to-date. 5. Correction of minor errors and internal inconsistencies. 6. Figure 1 (study schema) was corrected to remove reference to Blinded Independent Central Review (BICR). • Patient withdrawal due to disease progression will be based on the investigator's tumor response assessment, rather than BICR. 7. Section 9.3.2 was corrected to reflect that worsening of symptoms in the FBlSI-DRS-P subscale is measured as a decreased score (not an increase). In addition, the formal comparison of the Time to Deterioration endpoint between the two treatment arms for each of the co-primary populations was deleted so as not to inflate the overall type I error in the study. 8. Section 9.6 Interim Analysis was corrected to reflect that the timing of the

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		analysis will be based on deaths event and not disease progression events.
Original protocol	29 October 2015	Not Applicable (N/A)

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

PROTOCOL SUMMARY

Background and Rationale:

Urothelial cancer (UC) includes tumors originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra.[1] Bladder cancer alone accounts for 90% of UC,[1] and is the ninth most prevalent cancer worldwide, with approximately 400,000 new cases diagnosed and 150,000 deaths attributed to this disease each year.[2] UC occurs more frequently in developed countries; in Europe it is the eighth most common cause of mortality due to cancer, and in the United States, it also occurs at a very high annual incidence rate (20.5 per 100,000 persons).[3,4] The incidence and mortality of bladder cancer have remained unchanged over the last 25 years.[2]

Combination chemotherapy with platinum-based regimens is the standard of care for locally advanced or metastatic bladder cancer. Despite the favorable response and survival rates associated with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC),[10,11,12] toxicities associated with this regimen can be significant and lead to death in 3-4% of patients.[12,13] Subsequently, the combinations of gemcitabine + cisplatin and gemcitabine + carboplatin were shown to have comparable efficacy and an improved safety compared to MVAC,[14,15,16] with the latter combination used in the 30-50% of patients ineligible for cisplatin-based chemotherapy due to renal impairment.[17] As such, these two regimens are now the preferred regimens for the initial treatment of patients with locally advanced or metastatic UC.

Durable and complete responses following first-line chemotherapy in patients with advanced UC are uncommon. Complicated treatment regimens and severe side effects limit long-term use of these agents and most patients will ultimately experience disease progression within 9 months after initial response.[14] Optimal treatment in the second-line treatment setting still needs to be determined.[27] Single and combination agents evaluated in this treatment setting have been associated with low median progression-free survival (PFS, 1.5-3.0 months) and overall survival (OS, 4.6.-6.9 months), and are also associated with significant toxicities.[28,29,30]

In 2009, vinflunine was approved in Europe for the second-line treatment of UC after failure of first-line platinum-based therapy.[28,31]

The current "watch-and-wait" approach for the management of metastatic UC following response to first-line chemotherapy prior to initiation of second-line treatment has not proven to be effective because almost all patients eventually relapse. A multicenter Phase 2 study of sunitinib as maintenance therapy in patients with advanced UC was recently reported.[32] Although the study terminated prematurely due to low patient recruitment, it provided a different perspective on the treatment of this disease (ie, maintenance therapy following response to first-line chemotherapy in an attempt to improve the durability of the initial response). Recently, Powles et al reported the results of a Phase 2/3 study of lapatinib as maintenance treatment after first-line chemotherapy in patients with HER1/HER2-positive UC.[33] The median PFS, median OS, and objective response rate (ORR) for patients receiving lapatinib (n = 116) vs. placebo (n = 116) were 4.6 months (95% confidence interval

[CI]: 2.8 – 5.4) vs. 5.3 months (95% CI: 3.0 – 5.9) (hazard ratio [HR] 1.04 [95% CI: 0.79 – 1.39] p = 0.77), and 12.6 months (95% CI: 9.5 - 16.2) vs. 11.9 months (95% CI: 10.6 – 15.8) (HR 0.98 [95% CI: 0.71 – 1.35] p = 0.89); and 13.8% vs. 7.8%, respectively (p = 0.14). In addition, a study evaluating vinflunine[34,35] as a maintenance UC treatment is currently ongoing.

There is a strong rationale for considering immunotherapy in patients with advanced UC. Urologists led the way in the use of immunotherapy in cancer in 1976, having introduced the tuberculosis vaccine bacille Calmette-Guérin (BCG), which stimulates a robust immune response in most patients and has become the standard of care as locoregional therapy after surgical resection of non-muscle-invasive disease.[36,37] Multiple immunotherapies including interferon (IFN)-α, interleukin (IL)-2, IL-12, and IL-10 have been investigated, either as adjuncts with BCG or as a solo replacement therapy.[38,39] Over the past 40 years, progress evaluating immunotherapy for bladder cancer has been slow. Subsequently, the programmed cell death-1 (PD-1) / programmed death ligand 1 (PD-L1) pathway has emerged as an important biological pathway in UC.[40,41,42] PD-1, an immunoinhibitory receptor of the CD28 family, plays an important role in tumor immune escape.[43,44] The PD-1/PD-L1 interaction inhibits T-lymphocyte activation, proliferation, survival and effector functions during anti-cancer immune response. Several tumors, including UC, present with high rates of somatic mutations,[45,46,47] possibly enhancing the host immune system's ability to recognize tumor cells as foreign owing to an increased number of antigens and stimulate T-cell response.[48] However, these cancers may also elude immune surveillance and eradication through the expression of PD-L1 in the tumor microenvironment,[49] which then becomes an important target for anti-PD-L1 antibodies. Indeed, antibodies blocking PD-1 and PD-L1 have demonstrated significant and durable response in patients with advanced UC. In a Phase 1b study of anti-PD-1 mAb pembrolizumab in heavily pre-treated patients with advanced UC,[40] the ORR was 24% (10% complete response [CR] rate) among 33 treated patients with median follow-up duration of 11 months (range 10-13). The responses observed were durable, ranging from 16 to 40+ weeks (median not reached), with several responses ongoing at the time of analysis.

Similarly, an anti-PD-L1 mAb, MPDL-3280A, recently demonstrated significant durable response in heavily pre-treated patients with UC.[41,42] Preliminary data presented at the American Society of Clinical Oncology (ASCO) 2014 Annual Meeting from a Phase 1 study of MPDL3280A as second-line treatment of patients with UC demonstrated noteworthy activity in 20 evaluable patients with an ORR of 50%, including 1 CR and 9 partial responses (PRs).[41] Durable responses were also demonstrated with this agent in heavily pre-treated patients with advanced stage UC,[41,42] with an ORR of 54% in 68 patients with PD-L1-positive tumors, with durable ongoing responses up to 30.3 weeks reported.[41] Updated data from these studies with MPDL-3280A and pembrolizumab in patients with recurrent or metastatic PD-L1-positive UC further indicated durable responses with promising PFS and OS in patients with PD-L1-positive tumors, local immune/inflammatory cells, or stroma. Among 85 patients (46 PD-L1 immunohistochemistry [IHC] 2/3 and 38 IHC 0/1) with UC who received MPDL-3280A, the ORR for PD-L1 IHC 2+/3+ UC patients was 46% (95% CI: 31-61%; 6 CRs, 15 PRs) and IHC 0/1+ UC patients was 16% (95% CI 6-31%; 6 PRs); median response durations not reached (IHC 2/3 0+ to 54+

weeks; IHC 0/1 4+ to 33+ weeks). Median PFS for IHC 2+/3+ UC patients was 24 weeks (95% CI 12-NE) and for IHC 0/1+ UC patients was 8 weeks (95% CI 6-12).[50] Among 33 patients enrolled with ≥1% PD-L1-positive cells in tumor nests or a PD-L1-positive band in stroma by IHC to receive pembrolizumab, 28 had measurable disease at baseline. In these evaluable patients, the ORR was 25% (95% CI: 11-45), with 3 (11%) CR and 4 (14%) PR, with durations ranging from 16 to 50+ weeks (median not reached at time of analysis).[51]

Avelumab (MSB0010718C), a potent and highly selective fully human mAb of the immunoglobulin (Ig) G1 isotype, targets and binds PD-L1, the ligand for PD-1 and B7.1, thereby blocking the interaction between PD-L1 and PD-1 and B7.1, removing the suppressive effects of PD-L1 on anti-tumor CD8+ T cells and resulting in restoration of the cytotoxic T-cell response.[19]

In the Phase 1 study EMR 100070-001, 53 patients have been treated with avelumab doses of 1.0, 3.0, 10.0, and 20.0 mg/kg administered intravenous (IV) Q2W in the dose escalation phase. The 10 mg/kg dose level was selected for further study and a summary of pooled safety data from 1738 patients treated at this dose level in studies EMR 100070-001 and EMR 100070-003 (N=1738) is available with a data cutoff date of 09 June 2016.[19] The most frequently reported (incidence >5%) treatment-related adverse events were fatigue (17.7%), infusion-related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

Updated data from a pooled analysis of 249 patients enrolled in two advanced UC expansion cohorts in study EMR 100070-001 was recently published.[75] Patients were included regardless of PD-L1 expression levels. The median age was 68 years and 124 (50%) patients received 2 or more prior treatments for advanced or metastatic disease. At the time of the analysis (09 June 2016 data cut-off), the median follow-up was 9.9 months (range 4.3-12.1 months) and 60 (24%) patients were still on treatment. Among 161 post-platinum treated patients with at least 6 months of follow-up, the ORR was 17% (95% CI: 11-24%), including 9 CRs and 18 PRs. The disease control rate (DCR) was 40%, including 37 patients who had SD as their best response. An analysis using a cut-off of ≥5% for the expression of PD-L1 on tumor cells in 139 evaluable patients showed a 24% (15/63) ORR in the PD-L1 positive population and 13% (10/76) in the PD-L1 negative population, supporting that avelumab has anti-tumor activity in both the PD-L1 positive and negative populations. The median PFS was 11.9 weeks (95% CI: 6.1-18.0 weeks) and 6.1 weeks (95% CI: 5.9-8.0 weeks) in the PD-L1 positive and negative populations, respectively. The median OS was 8.2 months (95% CI: 5.7-13.7 months) and 6.2 months (95% CI: 4.3-14.0 months) in patients with PD-L1 positive and negative tumors, respectively.

These data support further evaluation of avelumab for the treatment of patients with advanced stage UC. Given the poor prognosis for patients with advanced UC whose disease progresses after first-line chemotherapy, where patient outcomes are ultimately very poor,[30,53,75] a maintenance treatment with avelumab after first-line platinum-based chemotherapy may provide additional clinical benefit compared to the current watch-and-wait standard of care after chemotherapy. The safety and efficacy of avelumab plus best supportive care (BSC, Arm A) and BSC alone (Arm B) will be evaluated in two

coprimary populations: 1) patients with PD-L1-positive tumors (including infiltrating immune cells) confirmed by a verified Good Manufacturing Practice (GMP) PD-L1 IHC test, and 2) all randomized patients to assess the effects of avelumab in this therapeutic setting.

Study Objectives:

Primary Objective

To demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging overall survival (OS) in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary UC patient population: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

Secondary Objectives

- To compare the PFS of avelumab plus BSC vs. BSC alone in patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and in all randomized patients.
- To evaluate the anti-tumor activity of avelumab plus BSC and BSC alone according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and in all randomized patients.
- To evaluate the overall safety profile of avelumab plus BSC and BSC alone.
- To evaluate the pharmacokinetics (PK) of avelumab in each of the co-primary populations treated with avelumab.
- To assess the immunogenicity of avelumab in each of the co-primary populations treated with avelumab.
- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in pre-treatment tumor tissue in each of the co-primary populations treated with avelumab.
- To evaluate the effect of avelumab plus BSC and BSC alone on patient-reported outcomes (PROs) in each of the co-primary populations.

Exploratory Objectives

- To explore the predictive and/or pharmacodynamic (PD) characteristics of peripheral blood and additional tumor tissue biomarkers relevant to the mechanism of action of or resistance to avelumab.

Study Endpoints:

Primary Endpoint

- Overall Survival (OS).

Secondary Endpoints

- Progression-free survival (PFS) based on Blinded Independent Central Review (BICR) assessment per RECIST v1.1.
- Investigator-assessed Progression-Free Survival (PFS). Objective Response (OR), Time to Tumor Response (TTR), Duration of Response (DR), and Disease Control (DC), as assessed per RECIST v1.1 by BICR and investigator.
- *Safety:* Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03; vital signs (blood pressure, pulse rate).
- *Pharmacokinetics (PK)*: maximum concentrations (C_{max}) and trough concentrations (C_{trough}) for avelumab.
- *Immunogenicity:* Anti-drug antibodies (ADA; neutralizing antibody [Nab]) against avelumab.
- *Biomarkers*: Tumor tissue biomarkers including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T lymphocytes.
- *Patient-Reported Outcomes:* patient-reported bladder cancer symptom, functioning, global quality of life (QOL), and Time to Deterioration (TTD) using the NCCN-FACT FBlSI-18; and health status using the EQ-5D-5L.

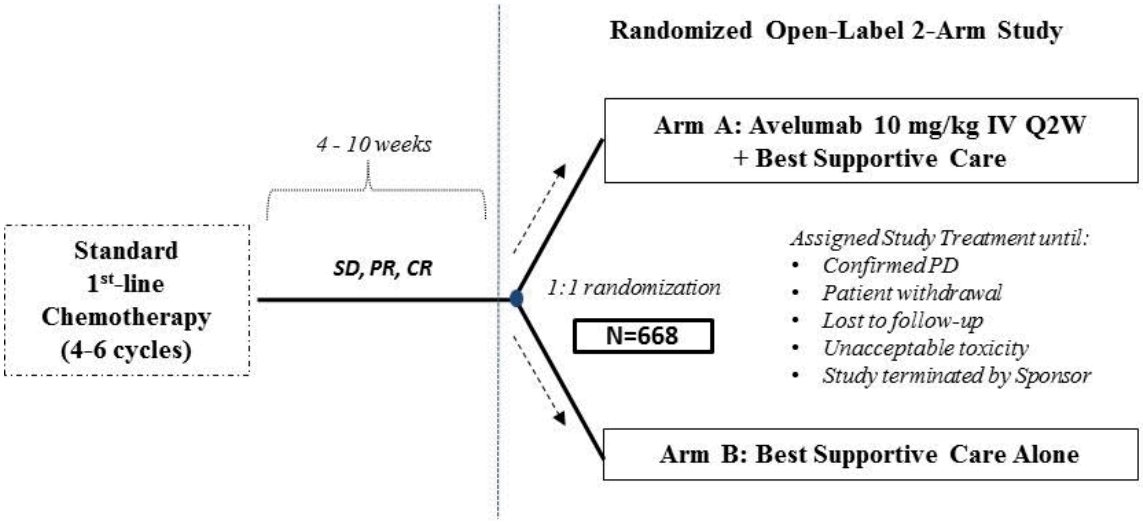
Exploratory Endpoints

- *Biomarkers:* Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to anti-tumor immune response and/or response to or disease progression on avelumab, such as genes related to IFN-γ or transforming growth factor (TGF)-β.

Study Design:

This is a Phase 3, multicenter, multinational, randomized, open-label, parallel-arm efficacy and safety study of avelumab plus BSC compared to BSC alone as a maintenance treatment after completion of first-line platinum-based chemotherapy (gemcitabine + cisplatin or gemcitabine + carboplatin) without evidence of disease progression in adult patients with unresectable locally advanced or metastatic UC.

The study design is illustrated in the following figure.



a. Allowed first-line chemotherapy regimens are gemcitabine + cisplatin or gemcitabine + carboplatin.
b. Randomization must occur at least 4 and not more than 10 weeks after the last dose of first-line chemotherapy and will be stratified by: best response on 1st-line therapy (CR or PR vs. SD) and metastatic disease site (visceral vs. non-visceral).

CR = complete response; IV = intravenous; PD = progressive disease; PR = partial response; Q2W = every 2 weeks; SD = stable disease

Patients may sign informed consent at any time during or after completion of chemotherapy and prior to any study specific procedures, however must meet all eligibility requirements to be randomized in the study.

- A total of approximately 668 patients without progressive disease as per RECIST v1.1 guidelines (ie, with ongoing CR, PR, or SD) after 1st line chemotherapy will be allowed to be randomized in this study. It is estimated that at least 334 patients with confirmed PD-L1-positive tumors (including infiltrating immune cells) will be randomized in this study.

- Patients will be randomized in a 1:1 ratio into two study arms: avelumab plus BSC (Arm A) or BSC alone (Arm B).

- Patients must have received at least 4 cycles, but not more than 6 cycles of a first-line chemotherapy regimen consisting of either gemcitabine + cisplatin or gemcitabine + carboplatin before randomization into this study. No other chemotherapy regimen is allowed as the first line chemotherapy for inclusion in this clinical trial (please see Section 4.1, Inclusion Criterion #2).

- Randomization must occur at least 4 but not more than 10 weeks after the date of administration of the last dose of chemotherapy. Patients will initiate study treatment (Cycle 1 Day 1) within 3 days after randomization.

- Only patients without progressive disease as per RECIST v1.1 guidelines (ie, with ongoing CR, PR, or SD) after 4-6 cycles of chemotherapy will be allowed to be randomized in this study.

    - Post-chemotherapy confirmatory scan(s) (computed tomography (CT)/magnetic resonance imaging (MRI)) for eligibility must be performed within 28 days prior to the date of randomization to assess response status following first-line chemotherapy.

    - Based on the post-chemotherapy confirmatory scan(s), the investigator should assess patient eligibility (ie, CR, PR, or SD) before randomization.

- This study is designed with two co-primary populations: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

- Randomization will be stratified by (i) best response to first-line chemotherapy (CR/PR vs. SD), and (ii) metastatic disease site (visceral vs. non-visceral) at the time of initiating first-line chemotherapy.

- Radiological tumor assessments will be conducted during the study at baseline as the post-chemotherapy confirmatory scan (as described above, within 28 days prior to randomization), at 8 weeks after randomization, then every 8 (±3 days) weeks for up to 1 year from randomization, and every 12 (±3 days) weeks thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Please see Section 3.1.2, Tumor Assessments for additional information.

- All patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of new anti-cancer therapy(ies). Long-term follow-up survival assessments (every 3 months) may be completed at the investigative site or by telephone contact.

- Upon approval of protocol Amendment 5, patients assigned to Arm B (BSC alone) who are progression-free and have not yet completed the End of Treatment (EOT) visit will be offered treatment with avelumab plus BSC maintenance therapy. For additional information, including Schedule of Activities for those patients who crossover to avelumab, please refer to Supplement 1.

- Arm B patients who do not crossover to avelumab plus BSC will continue assessments as per protocol.

- As per Protocol Amendment 6, following the final OS update, the frequency of study procedures will be reduced while providing continued treatment for patients actively

receiving avelumab and ending study participation for all patients who are not actively receiving avelumab (ie, Arm A patients in long-term follow-up and all Arm B patients who have not crossed over to receive avelumab).

Study Treatment:

- For the purpose of this study, "study treatment" refers to both the investigational product (avelumab) plus BSC and BSC alone administered to patients during participation in this study.
- Study treatments may continue until confirmed disease progression as assessed by BICR, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Patient Withdrawal).
- According to the opinion of an investigator, if a patient in Arm A is still experiencing clinical benefit at the time of confirmed disease progression, the patient will be eligible for continued treatment with avelumab plus BSC, provided the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.4.1 Treatment after Initial Evidence of Radiologic Disease Progression). Radiological tumor assessments will be continued in these patients as described in the Section 3.1.2, Tumor Assessments.
- If a patient starts a new anti-cancer therapy before documented disease progression, then tumor assessments should be continued per the Schedule of Activities (unless not feasible) until documentation of disease progression or death, whichever occurs first.
- After review of radiologic images by BICR is stopped as per Protocol Amendment 6, following the final OS update, study treatment may continue until disease progression is assessed by the investigator, patient refusal, patient lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Patient Withdrawal).

Arm A: Avelumab (MSB0010718C) Plus Best Supportive Care

Patients randomized to avelumab plus BSC (Arm A) will be administered avelumab as a 1-hour intravenous (IV) infusion at a dose of 10 mg/kg once every 2 weeks (Q2W) together with BSC (see below).

To mitigate potential infusion-related reactions, patients in Arm A will be premedicated prior to avelumab administration as described in Section 5.4.3.1. If an infusion-related reaction is observed, the infusion rate should be decreased or stopped depending on the severity of the event; please refer to Section 5.4.3.2 for further guidance.

Arm B: Best Supportive Care Alone

Patients randomized to BSC alone (Arm B) will be cared for as deemed appropriate by the treating physician. This could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC does not include any active anti-tumor therapy (see Section 5.8), however local radiotherapy of isolated lesions with palliative intent is acceptable as described in Section 5.9.2.

Statistical Methods:

The primary objective of this study is to demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging OS in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary UC patient populations: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

The study will randomize a total of approximately 668 patients, with at least 334 patients with confirmed PD-L1-positive tumors, using 1:1 randomization, stratified by best response to chemotherapy (CR/PR vs. SD) and site of metastasis (visceral vs. non-visceral) at time of initiating first-line chemotherapy.

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

- For all patients and patients with PD-L1-positive tumors receiving BSC alone after first-line chemotherapy, the median OS is 12 months.[33]
- For all patients receiving avelumab plus BSC after first-line chemotherapy, the median OS is assumed to be 17.1 months.
- For patients with PD-L1-positive tumors receiving avelumab plus BSC after first-line chemotherapy, the median OS is assumed to be 18.5 months.

This corresponds to a hazard ratio (HR) of 0.7 for all patients and 0.65 for patients with PD-L1-positive tumors under the exponential model assumption.

For all patients, if the true HR is 0.7 under the alternative hypothesis, a total of 425 OS events will be required to have 93% power to detect a HR of 0.7 using a one-sided log rank test at a significance level of 0.015 and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming)[71] α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

For patients with PD-L1 positive tumors, if the true HR is 0.65 under the alternative hypothesis, then a total of 219 OS events will be required to have 80% power to detect a HR of 0.65 using a one-sided log rank test at a significance level of 0.01 and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming)[71] α-spending function to determine

the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

The sample size further assumes a 5% drop-out rate for OS on either treatment arm, a non-uniform patient accrual accomplished over a 28-month period, and follow-up for about 11 months after the last patient is randomized. The data cutoff for the primary OS analysis will occur after the target number of events has been reached in both co-primary populations and the last patient randomized in the study has been followed for at least 12 months after randomization.

The study will be considered positive if the stratified log-rank test for OS is significant at the respective levels specified above at the time of the final analysis for either of the two co-primary populations.

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.

If deemed clinically necessary, the investigator may schedule visits in addition to those listed in the Schedule of Activities table (unplanned visits) at any time to conduct evaluations or assessments required to protect the well-being of the patient.

PRIOR TO PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR SCREENING AND STUDY TREATMENT PERIODS

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 4 weeks)			
		Arm A		Arm B	
	Within 28 Days Prior to Randomization	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles
Clinical Assessments					
Informed Consent[2]	X				
Medical/Oncological History[3]	X				
Baseline Signs/Symptoms[4]		X (Cycle 1 only)		X (Cycle 1 only)	
Physical Examination[5]	X	X		X	
ECOG Performance Status	X	X		X	
Vital Signs and Weight[6]	X	X	X	X	
Contraception Check[7]	X	X	X		
Laboratory Studies					
Coagulation[8]	X	X	X	X	
Hematology[8]	X	X	X	X	
Blood Chemistry (full and core)[8,9]	X	X[8,9]	X[8,9]	X[8,9]	
Thyroid Function and ACTH Tests[10]	X	X (at Cycles 3, 5, 7, etc.)		X (at Cycles 3, 5, 7, etc.)	
Serum/Urine Pregnancy Test[11]	X	X	X		
Troponin[12]	X	X (Cycles 1-4 and as clinically indicated)	X (Cycles 1-3 and as clinically indicated)	X (Cycles 1-4 and as clinically indicated)	
HBV, HCV Tests	X	If clinically indicated		If clinically indicated	
HIV test[13]	X				
Urinalysis[14]	X	If clinically indicated		If clinically indicated	
12-Lead ECG[15]	X	If clinically indicated		If clinically indicated	
Disease Assessments					
Tumor Assessments (including scans)[16]	X	X (Q8W for the 1st yr after randomization and Q12W thereafter)		X (Q8W for the 1st yr after randomization and Q12W thereafter)	
Other Clinical Assessments					
Adverse Events[17]		X	X	X	X[18]
Concomitant Medications/Treatments[19]	X	X	X	X	X[18]

Visit Identifiers[1]	Screening	Study Treatment (1 cycle = 4 weeks)			
		Arm A		Arm B	
	Within 28 Days Prior to Randomization	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles	Cycle 1 Day 1 Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All Cycles
Patient Reported Outcomes (NCCN-FACT FBlSI-18, EQ-5D-5L)[20]		X		X	
Randomization & Study Treatment					
Randomization[21]	X				
Avelumab (Arm A only)[22]		X	X		
Best Supportive Care (BSC)[23]		X (Throughout study treatment)		X (Throughout study treatment)	
Other Samplings					
Archival FFPE Tumor Tissue[24]	X				
Mandatory Recent FFPE Tumor Tissue Block or *de novo* biopsy[25]	X				
Banked Blood Biospecimen for Genotyping[26]		X (Cycle 1 only)		X (Cycle 1 only)	
Banked Blood Biospecimens for Exploratory Assessments[27]		X (Cycle 1, 2, 3 & 5)	X (Cycle 1 only)	X (Cycle 1, 2, 3 & 5)	
Pharmacokinetics[28]		X (Cycles 1-3, 5, 7, 9, 11 & 13)	X (Cycles 1-3)		
Anti-Avelumab Antibodies and Neutralizing Antibodies[29]		X (Cycles 1-3, 5, 7, 9, 11 & 13)	X (Cycles 1-3)		

ACTH = adrenocorticotropic hormone; BSC = best supportive care; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetics; Q12W = every 12 weeks

Footnotes for PRIOR TO PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR SCREENING AND STUDY TREATMENT PERIODS
1. **Visit Identifiers:** All assessments should be performed prior to dosing with study treatments unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. **Note**: laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure. May be obtained at any time during or after completion of first-line chemotherapy (ie, prior to 28-day screening period).

3.	**Medical/Oncological History:** To include information on prior adjuvant or neoadjuvant treatments, surgery, and radiation therapy. Information for the first-line chemotherapy regimen for advanced/metastatic disease will include planned doses, actual doses, and dates of administration. All sites of disease prior to first-line chemotherapy must also be documented.
4.	**Baseline Signs/Symptoms:** To be recorded on Cycle 1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to randomization.
5.	**Physical Examination:** Includes an examination of major body systems (height included at screening only).
6.	**Vital Signs and Weight:** Vital signs to include blood pressure and pulse rate, which should be taken prior to study drug dosing (if applicable) and with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes. Weight should be measured at each visit as indicated. For Arm A patients, weight should be measured within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]).
7.	**Contraception Check:** Female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use the selected contraception methods consistently and correctly and document such conversations in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the male patient's partner. After randomization, contraception checks will be performed only for Arm A patients. See Section 4.3.1.
8.	**Coagulation, Hematology, and Blood Chemistry (full panel)**: Required tests are listed in Table 6. Full chemistry panel is required at Screening, Cycle 1 Day 1, Cycle 1 Day 15 (Arm A patients), Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every 2 cycles (8 weeks) thereafter. May also be performed when clinically indicated. If full and core chemistry panels are scheduled at the same visit, only the full chemistry will be performed.
9.	**Blood Chemistry (core panel)**: Core chemistry panel (required tests are listed in Table 6) is required at each clinic visit at which a full chemistry panel is not required.
10.	**Thyroid Function and ACTH Tests:** Free T4, TSH, and ACTH tests will be performed at screening, Cycle 3 Day 1, and Day 1 of every 2 cycles (8 weeks) thereafter. Additional tests should be performed when clinically indicated. See Table 6.
11.	**Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study treatment: once at the start of screening and once at the Cycle 1 Day 1 visit for Arm A patients immediately before study treatment administration. Additional pregnancy tests (serum or urine) will also be routinely repeated for Arm A patients prior to each avelumab dose during the active treatment period, at the End of Treatment/Withdrawal visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. Results of the pregnancy test should be available prior to each dosing. After randomization, pregnancy tests will be performed only for Arm A patients. See Section 7.1.1.
12.	**Cardiac Troponin (cTn):** Measurement of cTnT is preferred; however, cTnI may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured during screening should be measured consistently throughout the study for any given patient. During screening, clinically significant positive results should be further assessed as per local standard of care to rule out concurrent cardiac conditions which could make the patient ineligible for the study per the exclusion criteria. During the study, clinically significant new elevations suggestive of myocarditis should be assessed as per Table 5. Additional tests should also be performed when clinically indicated. See Table 6.
13.	**HIV test:** HIV serology test is required at screening unless not permitted by local laws and regulations. If indicated, supplemental testing may be performed per standard practice to confirm an HIV infection.
14.	**Urinalysis**: Required only at Screening and End of Treatment. To be performed as clinically indicated at other time points. Required tests are listed in Table 6.

15. **12-Lead Electrocardiogram (ECG):** All patients require a single ECG measurement at screening. Additional ECGs may be performed as clinically indicated. Clinically significant new findings seen on follow-up ECGs should be recorded as adverse events.

16. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. Bone imaging, eg, bone scans or other methods considered standard of care locally, such as 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET) or MRI, are required at baseline. (**Note**: ^{18}FDG-PET may not be a permissible alternate for bone imaging at some centers or countries (eg, investigative sites in Canada)). Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone imaging will only be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of complete response (CR) confirmation, and at every other tumor assessment visit (ie, every 16 weeks for the first year after randomization and every 24 weeks thereafter) if considered local standard of care.

    Brain imaging (eg, MRI) is required at baseline for patients who have a history of brain metastases or for whom brain metastases are suspected during screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases at baseline; otherwise brain will only be evaluated when clinically indicated.

    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. All radiographic images from the time of the most recent tumor assessment prior to first-line chemotherapy until documented disease progression will be submitted to an independent third-party core imaging laboratory for Blinded Independent Central Review (BICR) as described in the Study Manual.

    For all patients, anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline (including chest, abdomen, and pelvic CT or MRI scans), at 8 weeks after randomization, then every 8 (±3 days) weeks for up to 1 year from randomization, and every 12 weeks (±3 days) thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

    Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 (Appendix 2). Complete response (CR) and partial response (PR) must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. See Section 7.7 for additional information.

17. **Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment (Arm A) or 90 days after the End of Treatment (EOT) visit (Arm B). SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor.

    AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least 1 dose of study treatment (Arm A) or from Cycle 1 Day 1(Arm B), through and including 90 calendar days after the last administration of the study drug (Arm A) or 90 days after the EOT visit (Arm B).

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
18. Day 15 Assessments for Arm B: Remote contact (eg, telephone) or in-clinic visit for collection of interim AEs and changes in concomitant medications and treatments, if any. A follow-up in-clinic visit should be scheduled if clinically indicated.
19. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded for all patients from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (Arm A) or 90 days after the EOT visit (Arm B). If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new cancer therapy is started; see Section 5.9 for additional details. All concomitant medications will be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant medications should be reviewed at each study visit, and any prohibited treatments (as described in Section 5.9) should be discussed with the patient and appropriately managed.
20. NCCN-FACT FBlSI-18, EQ-5D-5L: All patients will complete these self-administered questionnaires on Day 1 of each cycle. Patients must complete each questionnaire at the clinic prior to any study or medical procedure.
21. **Randomization:** An interactive response technology (IRT) system will be used for randomization to a treatment arm as described in Section 5.1. Patients meeting all entry criteria will be randomized and, if randomized to Arm A, will be administered the first dose of avelumab within 3 days after randomization.
22. **Avelumab Study Treatment (Arm A):** For patients randomized to Arm A, avelumab (10 mg/kg) will be given as a 1-hour intravenous infusion every 2 weeks. Patients should be weighed within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]). All safety assessments must be performed and results reviewed by the treating physician prior to study treatment administration. Patients with disease progression who are continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.4.1).
23. Best supportive care (BSC): All patients (Arm A and Arm B) will receive BSC during this study, as described in Section 5.8. All BSC components must comply with the permitted medications described in this protocol (see Section 5.9).
24. **Archival FFPE Tumor Tissue:** An archival formalin fixed, paraffin embedded (FFPE) tumor tissue block (or subsection thereof) collected at the time of primary diagnosis or first tumor resection (if different from the most recent sample described in footnote 25) is strongly encouraged to assess changes in the tumor microenvironment relative to the most recent sample. If an FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable. A sample from a later timepoint that is still prior to the most recent tumor tissue sample (see footnote 25) may be substituted, if necessary. Tumor tissue from cytologic samples (eg, FFPE cell pellet from Fine Needle Aspiration biopsy) or bone metastases are not acceptable. See Section 6.1.1 and Section 7.5.1.
25. **Mandatory Recent FFPE Tumor Tissue Block or *de novo* biopsy:** All patients must provide an FFPE tumor tissue block (or subsection thereof) from the most recent primary or metastatic tumor biopsy or resection obtained prior to treatment with first line chemotherapy but within 24 months prior to randomization, with no intervening systemic anti-cancer therapy between the time the tissue was obtained and initiation of first-line chemotherapy. If an FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or bone metastases is not adequate and should not be submitted. If a suitable tissue sample is not otherwise available, then an FFPE tissue sample from a *de novo* biopsy (core needle or excisional) must be obtained for research purposes (ie, after informed consent has been obtained and prior to randomization). See Section 6.1.1 and Section 7.5.1. **Note:** This mandatory tumor tissue sample must be submitted to the Central Laboratory prior to randomization.

26.	**Banked Blood Biospecimen for Genotyping**: A single 4-mL blood sample will be collected on or prior to Cycle 1 Day 1 (prior to dosing for Arm A patients and at any time for Arm B patients) and retained in a biobank for possible pharmacogenetic assessments (ie, genotyping), unless prohibited by local regulations or by decision of the institutional review board or ethics committee. See Section 7.6 for further details.
27.	**Banked Blood Biospecimens for Exploratory Assessments:** Blood biospecimens (~24 mL) will be collected and retained as whole blood, plasma, and serum specimens (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis; Prep B1: 10 mL K_2 EDTA blood for plasma preparation, and Prep B2: 10 mL blood for serum preparation) in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. For all patients, samples will be collected on or prior to Cycle 1 Day 1, and on Day 1 of Cycles 2, 3, and 5 (all pre-dose). An additional sample timepoint will include pre-dose on Cycle 1 Day 15 for Arm A patients. See Section 7.5.2 and Section 7.6.
28.	**Pharmacokinetics**: ARM A ONLY: Blood samples (3.5 mL) for avelumab PK will be collected pre-dose and at the end of infusion (immediately before the end of avelumab infusion) on Day 1 and Day 15 of Cycles 1 – 3, and then pre-dose and at the end of infusion (immediately before the end of avelumab infusion) on Day 1 of Cycle 5, 7, 9, 11 and 13. Do not collect blood from the same arm being infused. See Section 7.3 for further details.
29.	**Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab):** Arm A ONLY: One blood sample (3.5 mL) for anti-avelumab antibodies will be collected pre-dose on Day 1 and Day 15 of Cycles 1 – 3, and then on Day 1 of Cycle 5, 7, 9, 11 and 13. All samples should be drawn within 2 hours before the start of avelumab infusion. All samples that are positive for ADA may also undergo characterization for Nab. See Section 7.4.

PRIOR TO PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR END OF TREATMENT/WITHDRAWAL AND FOLLOW-UP PERIODS

Visit Identifiers[1]	End of Treatment/ Withdrawal (±3 days)[2]	Follow-up[3]			
		Short-Term			Long-Term every 3 months ±14 days)
		30 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	60 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	90 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	
Documentation					
Physical Examination[4]	X	X	X	X	
ECOG Performance Status	X	X	X	X	
Vital Signs and Weight[5]	X	X	X	X	
Contraception Check (Arm A ONLY)[6]	X	X			
Laboratory Studies					
Hematology[7]	X	X	X	X	
Blood Chemistry (full panel)[8]	X	X	X	X	
Coagulation[7]	X	X	X	X	
Thyroid Function Tests and ACTH[9]	X	X	X	X	
Serum/Urine Pregnancy Test (Arm A ONLY)[10]	X	X			
Urinalysis[11]	X				
12-lead ECG[12]	If clinically indicated				
Disease Assessments					
Tumor Assessments (including scans)[13]	X (Q8W for the 1st year after randomization and Q12W thereafter)				
Other Clinical Assessments					
Adverse Events[14]	X	X	X	X	
Concomitant Medications/Treatments[15]	X	X	X	X	
New Systemic Anticancer Treatment	X	X	X	X	X
Survival Assessment[16]		X	X	X	X
Patient-Reported Outcomes (NCCN-FACT FBlSI-18, EQ-5D-5L)[17]	X	X	X	X	
Other Samplings					
Banked Blood Biospecimens for Exploratory Assessments[18]	X				
De Novo Tumor Biopsy[19]	X				

Visit Identifiers[1]	End of Treatment/ Withdrawal (±3 days)[2]	Follow-up[3]			
		Short-Term			Long-Term every 3 months ±14 days)
		30 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	60 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	90 days (±3 days) After Last Dose (Arm A) or EOT/Withdrawal Visit (Arm B)	
Pharmacokinetics[20] (Arm A ONLY)	X	X			
Anti-Avelumab Antibodies and Neutralizing[21] (Arm A ONLY)	X	X			

ACTH = adrenocorticotropic hormone; BSC = best supportive care; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; Q12W = every 12 weeks

Footnotes for PRIOR TO PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR END OF TREATMENT/WITHDRAWAL AND FOLLOW-UP PERIODS

1. **Visit Identifiers:** Acceptable time windows for performing each assessment are described in the column headers. Per the visit time window, laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.
2. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.
3. **Short- and Long-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment (Arm A) or 30 through 90 days after the End of Treatment (EOT) visit (Arm B), or until the time of initiation of new anticancer treatment. Beyond the 90 days until the end of the study (long-term follow-up), all patients will be followed every 3 months after the last study clinic visit (±14 days) for survival, tumor assessment, and new systemic anticancer treatment; additional timepoints to collect survival information may be requested by the Sponsor in preparation for interim and final analyses.
4. **Physical Examination:** Includes an examination of major body systems.
5. **Vital Signs and Weight:** Vital signs to include blood pressure and pulse rate. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
6. **Contraception Check** (Arm A patients)**:** Female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception until at least 30 days after the last dose of study treatment. The investigator or his or her designee will discuss with the patient the need to use the selected contraception methods consistently and correctly and document such conversations in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the male patient's partner. See Section 4.3.1.
7. **Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 6. May also be performed when clinically indicated.
8. **Blood Chemistry:** Full chemistry panel (see Table 6) is required at End of Treatment/Withdrawal and during short-term follow-up visits (Days 30 ±3, 60 ±3, 90 ±3 after last dose).
9. **Thyroid Function Tests:** Free T4, TSH, and ACTH will be performed at the End of Treatment/Withdrawal and at Follow-up visits at 30±3, 60±3, and 90 ±3 days after last dose. Additional tests should be performed when clinically indicated. See Table 6.

10. Serum/Urine Pregnancy Test (Arm A patients)**:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the End of Treatment/Withdrawal visit and at the 30-Day Follow-up visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. See Section 7.1.1.
11. Urinalysis: Required only at the End of Treatment/Withdrawal. To be performed as clinically indicated at other time points. Required tests are listed in Table 6.
12. 12-Lead Electrocardiogram (ECG): When clinically-indicated. Clinically significant new findings seen on follow-up ECGs should be recorded as adverse events. See Section 7.1.5 for further details.
13. **Tumor Assessments:** Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone imaging (eg, bone scans or other methods considered standard of care locally, such as ^{18}FDG-PET or MRI) will only be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of complete response (CR) confirmation, and at every other tumor assessment visit (ie, every 16 weeks for the first year after randomization and every 24 weeks thereafter) if considered local standard of care. (**Note**: ^{18}FDG-PET may not be a permissible alternate for bone imaging at some centers or countries (eg, investigative sites in Canada). Brain must be included in subsequent tumor assessments if a patient has brain metastases at baseline; otherwise brain will only be evaluated when clinically indicated. 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. All radiographic images from the time of the most recent tumor assessment prior to first-line chemotherapy until documented disease progression will be submitted to an independent third-party core imaging laboratory as described in the Study Manual. For all patients, anti-tumor activity will be assessed through radiological tumor assessments (including chest, abdomen, and pelvic CT or MRI scans) conducted every 8 weeks (± 3 days) for up to 1 year from randomization and every 12 weeks (±3 days) thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Assessment of response will be made using RECIST v.1.1 (Appendix 2). Complete response (CR) and partial response (PR) must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. See Section 7.7 for additional information.
14. **Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment (Arm A) or 90 days after the EOT visit (Arm B). SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least 1 dose of study treatment (Arm A) or from Cycle 1 Day 1 (Arm B), through and including 90 calendar days after the last administration of the study treatment (Arm A) or 90 days after the EOT visit (Arm B). If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
15. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded for all patients from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (Arm A) or 90 days after the EOT visit (Arm B). If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new cancer therapy is started; see Section 5.9 for additional details. All concomitant medications will be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).
16. **Survival Assessment:** All patients will be followed for survival and subsequent anticancer therapies every 3 months (±14 days) after the last study clinic visit until death, end of the study, or patient withdrawal of consent, whichever comes first. These visits may be conducted in-clinic or by remote contact (eg, telephone). Additional timepoints to collect survival information may be requested by the Sponsor in preparation for interim and final analyses.
17. Patient-Reported Outcome Questionnaire: NCCN-FACT FBlSI-18 and EQ-5D-5L are to be administered at the End of Treatment/Withdrawal visit and at the 30, 60 and 90 Day Follow-up Visits.
18. Banked Blood Biospecimens for Exploratory Assessments: Blood biospecimens (~24 mL) will be collected at the End of Treatment/Withdrawal visit and retained as whole blood, plasma, and serum (Prep D1: 4 mL K_2 EDTA whole blood collection optimized for DNA analysis; Prep B1: 10 mL K_2 EDTA blood for plasma preparation, and Prep B2: 10 mL blood for serum preparation), and retained in a biobank for exploratory biomarker assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. See Section 7.5.2 and Section 7.6.
19. *De Novo* Tumor Biopsy: A *de novo* (ie, fresh biopsy) tumor sample should also be collected at End of Treatment/Withdrawal visit, unless clinically contraindicated. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including formalin fixed, paraffin embedded [FFPE] cell pellet material) or bone metastases is not adequate and should not be submitted. The *de novo* biopsy should be formalin-fixed and paraffin-embedded as per routine procedures (see Laboratory Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. If an FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable.
20. Pharmacokinetics: Arm A ONLY: Blood samples (3.5 mL) for avelumab PK will be taken at the End of Treatment and 30 day Follow-up visits. Details are outlined in Section 7.3.
21. Anti-Avelumab Antibodies (Anti-Drug Antibodies, ADAs) and Neutralizing Antibodies (Nab): Arm A ONLY. One blood sample (3.5 mL) for anti-avelumab antibodies (and simultaneous pharmacokinetic draws for measurement of avelumab) will be collected at the End of Treatment and 30 day Follow-up visits. All the samples that are positive for ADA may also undergo characterization for Nab.

PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR STUDY TREATMENT, END OF TREATMENT AND FOLLOW-UP PERIODS

Visit Identifiers[1]	Avelumab plus BSC (1 cycle = 4 weeks)		End of Treatment/ Withdrawal (±3 days)[2]	Short-Term Follow-Up[3]		
	Day 1 (±3 days)	Day 15 (±3 days)		30 days (±3 days) After Last Dose of Avelumab	60 days (±3 days) After Last Dose of Avelumab	90 days (±3 days) After Last Dose of Avelumab
Clinical Assessments						
Physical Examination[4]	Assessment not required per protocol but may be performed as clinically necessary					
ECOG Performance Status[4]	Assessment not required per protocol but may be performed as clinically necessary					
Vital Signs [4]	Assessment not required per protocol but may be performed as clinically necessary					
Weight[5]	X	X				
Contraception Check[4,6]	X	X	X	X		
Laboratory Studies						
Hematology[4,7]	X	X	X	X	X	X
Blood Chemistry[4,7]	X	X	X	X	X	X
Thyroid Function and ACTH Tests[4,8]	X (at odd number cycle only)		X	X	X	X
Serum/Urine Pregnancy Test[4,9]	X	X	X	X		
Urinalysis[4]	Assessment not required per protocol but may be performed as clinically necessary					
12-Lead ECG[4,10]	Assessment not required per protocol but may be performed as clinically necessary					
Other Assessments						
Tumor Assessments (including scans)[11]	As per local standard of care and when progression is suspected					
Adverse Events[12]	X	X	X	X	X	X
Concomitant Medications/Treatments[13]	Assessment not required per protocol but may be performed as clinically necessary					
Study Treatment						
Avelumab[14]	X	X				

ACTH = adrenocorticotropic hormone; BSC = best supportive care; CR = crossover; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group

Footnotes for PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR SCREENING AND STUDY TREATMENT PERIOD

1.	**Visit Identifiers:** All assessments will be performed prior to dosing with avelumab unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. **Note**: laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.
2.	**End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week.
3.	**Short-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of avelumab or until the time of initiation of a new anticancer treatment, whichever occurs first.
4.	These data will not be captured in the CRF unless the findings support the reporting of an AE.
5.	**Weight:** Weight should be measured within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]).
6.	**Contraception Check:** Female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use the selected contraception methods consistently and correctly and document such conversations in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the male patient's partner. See Section 4.3.1.
7.	**Hematology and Blood Chemistry:** Required tests are listed in Table 7. May also be performed when clinically indicated.
8.	**Thyroid Function and ACTH Tests:** Free T4, TSH, and ACTH tests will be performed on Day 1 of every 2 cycles (8 weeks). Additional tests should be performed when clinically indicated. See Table 7.
9.	**Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be routinely repeated prior to each avelumab dose during the active treatment period, at the End of Treatment/Withdrawal visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. Results of the pregnancy test should be available prior to each dosing. See Section 7.1.1.
10.	**12-Lead Electrocardiogram (ECG):** To be performed as clinically indicated. Clinically significant new findings seen on follow-up ECGs should be recorded as adverse events.
11.	**Tumor Assessments:** Tumor assessments will be performed at a frequency as per local standard of care and when progression is suspected. The tumor assessment data will no longer be entered into the CRF and radiologic images will no longer be submitted for central imaging review.
12.	**Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor. AEs (serious and non-serious) should continue to be recorded on the Case Report Form (CRF) through and including 90 calendar days after the last administration of avelumab. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
13.	**Concomitant Medications/Treatments:** Concomitant medications and treatments should only be recorded in the CRF if associated with treatment for an AE.
14.	**Avelumab Treatment:** Avelumab (10 mg/kg) will be given as a 1 hour intravenous infusion every 2 weeks. Patients should be weighed within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]). All safety assessments must be performed and results reviewed by the treating physician prior to avelumab administration. Patients with disease progression who are continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.4.1).

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Avelumab selectively binds to programmed death-ligand 1 (PD-L1) and competitively blocks its interaction with programmed death protein 1 (PD-1). The mechanism of avelumab action is further described in Section 1.2.2.1.

The indication under study is the maintenance treatment of unresectable locally advanced or metastatic urothelial cancer (UC) after standard first-line platinum containing chemotherapy.

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.[1] Bladder cancer alone accounts for 90% of UC,[1] and is the ninth most prevalent cancer worldwide, with approximately 400,000 new cases diagnosed and 150,000 deaths attributed to this disease each year.[2] UC occurs more frequently in developed countries; in Europe it is the eighth most common cause of mortality due to cancer and occurs at a very high annual incidence rate (20.5 per 100,000 persons) in the United States.[3,4] The incidence and mortality of bladder cancer have remained unchanged over the last 25 years.[2]

Approximately 30% of patients with newly diagnosed UC present with muscle-invasive UC of the bladder,[5] a high-grade, typically aggressive disease requiring multimodal therapy including radical cystectomy and chemotherapy.[1,6,7] Metastatic disease is observed in 5% of patients at the time of diagnosis[6] or, if localized at diagnosis, metastasis develops within 2 years when treated with radical cystectomy alone.[8,9]

Combination chemotherapy with platinum-based regimens is the standard of care for locally advanced or metastatic bladder cancer. Despite the favorable response and survival rates associated with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC),[10,11,12] toxicities associated with this regimen can be significant and lead to death in 3-4% of patients.[12,13] Subsequently, the combinations of gemcitabine + cisplatin and gemcitabine + carboplatin were shown to have comparable efficacy and an improved safety compared to MVAC,[14,15,16] with the latter combination used in the 30-50% of patients ineligible for cisplatin-based chemotherapy due to renal impairment.[17] As such, these two regimens are now the preferred regimens for the initial treatment of patients with locally advanced or metastatic UC.

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

The investigational product in the present clinical trial is avelumab (MSB0010718C), a fully human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype.

Avelumab selectively binds to programmed death-ligand 1 (PD-L1) and competitively blocks its interaction with programmed death protein 1 (PD-1). Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[18] For complete details of the in vitro and nonclinical studies, refer to the Avelumab Investigator's Brochure.[19]

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono, and is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, Merkel cell carcinoma, renal cell carcinoma, ovarian cancer, and urothelial cancer.

Trial EMR100070-001 is a Phase 1, open-label, multiple-ascending dose clinical study aimed to investigate the safety, tolerability, pharmacokinetics (PK), biological activity, and clinical activity of avelumab in patients with metastatic or locally advanced solid tumors. This trial consists of 2 parts, a dose-escalation phase and a dose-expansion phase, which is performed in selected tumor indications. Avelumab is administered intravenously (IV) at the assigned dose level as a 1-hour infusion once every 2 weeks (Q2W). The following dose levels have been investigated: 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg, and 20.0 mg/kg.

As of 01 June 2015, 53 patients were treated in the dose-escalation phase of the EMR10070-001, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg, respectively. None of the patients treated with doses up to 10 mg/kg experienced a dose-limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well-tolerated dose for further investigation in the dose-expansion cohorts. One DLT (a Grade 3 immune-related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

As of 01 June 2015, 717 patients have been enrolled in the tumor type specific expansion cohorts and treated with the recommended dose of 10 mg/kg avelumab (Q2W); safety data were available for all of these patients as of the data cut-off date and are briefly summarized here.

Treatment-related treatment emergent adverse events (TEAEs) were observed in 498 (69.5%) subjects in the pooled expansion cohorts. The most frequently observed treatment-related TEAEs (with an incidence of ≥5%) of any grade were infusion-related reaction (18.7%), fatigue (18.1%), nausea (10.3%), diarrhea (6.8%), chills (6.7%), and decreased appetite (5.2%). The most frequently reported (incidence ≥5%) treatment-related TEAEs (any grade) in the pooled expansion cohort are summarized in Table 1. The most frequently reported (occurring in at least 3 patients) Grade ≥3 treatment-related TEAEs in the pooled expansion cohorts are presented in Table 2.

Table 1. Most Frequently Reported (Incidence ≥5%) Treatment-Related TEAEs in the Pooled Expansion Cohorts (Any Grade)

MedDRA Preferred Term	Pooled Expansion Cohort Patients (n=717) n (%)
Number of patients with at least 1 TEAE	498 (69.5%)
Infusion related reaction	134 (18.7%)
Fatigue	130 (18.1%)
Nausea	74 (10.3%)
Diarrhea	49 (6.8%)
Chills	48 (6.7%)
Decreased appetite	37 (5.2%)

Table 2. Most Frequently Reported (in ≥3 Patients) Grade ≥3 Investigational Product-Related TEAEs in the Pooled Expansion Cohorts

MedDRA Preferred Term	Pooled Expansion Cohort Patients (n=717) n (%)
Number of patients with at least 1 TEAE	77 (10.7%)
Gamma-glutamyltransferase increased	7 (1.0%)
Infusion related reaction	7 (1.0%)
Lipase increased	7 (1.0%)
Anemia	6 (0.8%)
Fatigue	5 (0.7%)
Aspartate aminotransferase increased	4 (0.6%)
Autoimmune hepatitis	4 (0.6%)
Alanine aminotransferase increased	3 (0.4%)
Lymphocyte count decreased	3 (0.4%)
Pneumonitis	3 (0.4%)

As of 01 June 2015, 289 of 717 patients (40.3%) in the pooled expansion cohorts had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 47 of these patients, and included infusion-related reaction and pneumonitis (each in 6 subjects; 0.8%), pyrexia (4 subjects; 0.6%), autoimmune hepatitis and dyspnea (each in 3 subjects; 0.4%), and colitis and non-cardiac chest pain (each in 2 subjects; 0.3%). All other treatment-related serious TEAEs were reported in a single subject (0.1%) only.

Among the 717 patients, 290 patients (40.4%) have died, mostly due to disease progression (216 deaths; 30.1%). Overall, a total of 4 deaths (0.6%) due to TEAEs related to study treatment were considered as the primary reason of the death by the investigator. Two additional cases of death were reported and assessed as treatment-related, but the treatment related TEAEs were not considered as the primary reason of the death. These 6 deaths due to TEAEs related to study treatment were attributed to the following events: pneumonitis radiation induced and dyspnea; acute liver failure associated with autoimmune hepatitis (no biopsy/autopsy performed); fatal anoxic brain injury (not related) after cardiac arrest (related); autoimmune hepatitis with hepatic failure and fatigue (no biopsy/autopsy

performed); respiratory distress and sepsis; and acute respiratory failure, acute exacerbation chronic obstructive pulmonary disease (COPD).

A total of 139 patients (19.4%) in the dose expansion cohorts withdrew permanently from study treatment due to TEAEs. In 60 (8.4%) of these patients, the TEAEs leading to study treatment discontinuation were considered to be related to study treatment by the investigator. The most frequent (≥2 patients) treatment-related TEAEs leading to discontinuation were infusion-related reaction (19 patients; 2.6%), gamma-glutamyltransferase increased (5 patients; 0.7%), autoimmune hepatitis, blood creatine phosphokinase increased, and lipase increased (3 patients; 0.4%), and dyspnea (2 patients; 0.3%).

Immune-related Adverse Events: As of 01 June 2015, a cumulative review identified 106 patients with potential immune-related adverse events (irAEs) out of 717 patients (14.8%) treated in the pooled expansion cohort of trial EMR 100070-001. Treatment-related potential irAEs were observed in 71 of the 717 patients (9.9%). Hypothyroidism was the most frequent treatment-related irAE, which occurred in 32 patients (4.5%) in the pooled expansion cohort. The other frequent irAEs, which were considered as treatment-related, were pneumonitis (8 patients; 1.1%), autoimmune hepatitis and hyperthyroidism (4 patients; 0.6%), and colitis and dry eye (3 patients each; 0.4%). Additional treatment-related irAEs were seen in 2 or 1 patients in the pooled expansion cohort.

Infusion-Related Reactions: Two suspected unexpected serious adverse reactions (SUSARs; anaphylactic reaction and infusion-related reaction) involving 2 patients were reported in December 2013 and triggered a cumulative review of serious and non-serious cases of infusion-related reactions and hypersensitivity across the avelumab program. Following evaluation of safety signals, infusion-related reactions and hypersensitivity were classified as a newly identified risk (previously classified as a potential risk) and a mandatory premedication regimen of a histamine H1 receptor (H1) blocker plus acetaminophen/paracetamol was implemented for all trial patients starting 29 January 2014.

As of 01 June 2015, 138 of 717 patients (19.2%) in the pooled expansion cohort experienced at least 1 episode of infusion-related reaction. Most of the events were Grade 1 (30 patients, 4.2%) or Grade 2 (101 patients, 14.1%) in intensity, and Grade 3 (5 patients, 0.7%) or Grade 4 events (2 patients, 0.3%) were less frequent. No Grade 5 events were reported. Most of the infusion-related reactions had an onset after the first (91 patients, 12.7%) or second (35 patients, 4.9%) avelumab infusion, and those with an onset after the third (9 patients, 1.3%) or fourth avelumab infusion (3 patients, 0.4%) were less frequent. In 17 patients (2.4%), avelumab treatment was discontinued because of infusion-related reaction.

After introduction of the mandatory premedication on 29 January 2014, 35 and 677 patients in the dose escalation and the pooled expansion cohorts of Trial EMR 100070-001 received trial treatment, respectively. Under this premedication procedure, 117 of 677 patients (17.3%) in the pooled expansion cohort experienced infusion-related reaction, with 28 patients (4.1%) having Grade 1, 86 patients (12.7%) having Grade 2, and 3 patients

(0.4%) having Grade 3 event. No Grade 4 infusion-related reaction was observed after introduction of the mandatory premedication. Three patients (8.6%) in the dose escalation cohort reported infusion-related reactions (all Grade 2) starting from 29 January 2014.

In addition to the aforementioned patients, 1 case of Grade 4 cardiac arrest occurred 1.5 hours after the third infusion of avelumab (10 mg/kg). The patient died due to anoxic brain injury 7 days later; no autopsy was performed.

The management of infusion-related reactions and severe hypersensitivity reactions can be found in Section 5.4.3.2. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf.

Myocarditis: As reported in the Investigator's Brochure,[19] three cases of myocarditis have been reported among patients receiving avelumab:

- A case of fatal myocarditis (case no. E2B_80035746) occurred in a patient enrolled in study B9991002, a Phase I study of avelumab in combination with axitinib in renal cell carcinoma. The event occurred 5 days after the second and 19 days after the first dose of avelumab (10 mg/kg).

- A case of non-fatal myocarditis (case no. 260076) was reported in the context of a Grade 3 autoimmune syndrome characterized by myositis and myocarditis in a patient enrolled in study EMR 100070-001, a Phase I study of avelumab in patients with advanced solid tumors. The event occurred 18 days after the first dose of avelumab (20 mg/kg).

- A fatal case of potential autoimmune myocarditis, acute cardiac failure and respiratory failure (case no. 8091934) occurred in a patient enrolled in study EMR 100070-004, a Phase III study of avelumab as a second-line treatment for non-small cell lung cancer. The events occurred 14 days after the first and only dose of avelumab (10 mg/kg).

Cases of severe or fatal myocarditis also have been reported with other immune checkpoint inhibitors, including pembrolizumab, nivolumab, and ipilimumab,[20-24] either as single adverse events or in the context of more complex autoimmume syndromes. For both ipilimumab and nivolumab, myocarditis is reported in the prescribing information with a frequency of <1%.[25,26]

Given these reports, routine troponin measurements are being implemented in selected avelumab studies, including Protocol B9991001. Cardiac troponin (cTn) is a sensitive marker of myocardial injury and may aid in the identification of patients potentially experiencing myocarditis; however, the utility of routine troponin monitoring for the early detection of myocarditis is currently unknown. In addition to cTn monitoring, guidelines for the management of suspected or confirmed myocarditis and relevant avelumab management instructions are provided in Table 5.

Avelumab Pharmacokinetics: Avelumab pharmacokinetics and dose proportionality following the first 1-hour infusion have been characterized in 77 mainly Caucasian patients treated in the dose escalation and expansion cohorts of Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of C_{max} and AUC_{τ} increased with dose in a linear fashion across the 1, 3, 10 and 20 mg/kg doses. The apparent half-life tends to increase with the dose, presumably linked to target-mediated disposition. Taking into account the variability, the half-lives of the 10 and 20 mg/kg doses were similar (mean half-lives of 102 and 120 hours, respectively), indicating that target mediated elimination does not increase at these doses. This implies that target occupancy is likely to be high at these two doses throughout the dosing interval.

Target occupancy on peripheral blood CD3+ T-cells was investigated in human blood from 8 healthy volunteers in vitro by flow cytometry after spiking of whole blood samples with avelumab over a concentration range of 0.003-10 μg/mL. Fifty percent (50%) receptor occupancy was observed at a drug concentration of 0.122 μg/mL ±0.042 μg/mL with a plateau indicating at least 95% receptor occupancy reached in all blood samples at 1 μg/mL. PK profiles obtained from the dose escalation phase of Study EMR 100070-001 found all patients at 10 mg/kg dose reached or exceeded the serum level (median C_{trough} 20-37 ug/ml) of avelumab required for >95% target occupancy. For patients treated with 3 mg/kg of avelumab, 10 of 13 patients reached the required serum level (3.7 - 8.3 μg/mL).

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the Avelumab Investigator's Brochure.[19]

1.2.2.2. Rationale for Best Supportive Care as Comparator Arm

Currently, there are no approved therapeutic agents for the maintenance treatment of patients with unresectable UC who have completed prior systemic therapy with a platinum-based regimen. Despite improvement of patient outcomes with these first-line therapies, durable and complete responses (CRs) in patients with advanced UC are uncommon and severe side effects limit long-term use of these agents. Following completion of first-line therapy, patients are managed with best supportive care (BSC) until disease progression. The "Guideline on the evaluation of anticancer medicinal products in man" (European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP)/205/95/Rev.4, Dec2012) indicates that BSC may be acceptable in cases where there is no well-documented reference regimen. This guideline also defines BSC to include antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc., but does not include active anti-tumor therapy.

1.2.3. Rationale for Studying Avelumab plus Best Supportive Care in Patients with Advanced Urothelial Cancer

1.2.3.1. Medical Need

Durable CR following first-line chemotherapy in patients with advanced UC are uncommon. Complicated treatment regimens and severe side effects limit long-term use of these agents and most patients will ultimately experience disease progression within 9 months after initial response.[14] Patients with stable disease (SD) or objective response (OR) are typically

managed with BSC alone after completion of first-line chemotherapy until progression of disease occurs and only then begin treatment with an alternate therapy. While platinum-based combination chemotherapy leads to high response rates in patients with UC, most patients will ultimately experience disease progression. Optimal treatment in the second-line treatment setting still needs to be determined.[27] Single and combination agents evaluated in this treatment setting have been associated with low median progression-free survival (PFS, 1.5-3.0 months) and overall survival (OS, 4.6.-6.9 months), and are also associated with significant toxicities.[28,29,30]

In 2009, vinflunine was approved in Europe for the second-line treatment of UC after failure of first-line platinum-based therapy.[28,31] Three hundred seventy (370) adult patients with advanced or metastatic transitional-cell carcinoma of the urothelial tract were randomly assigned 2:1 to vinflunine plus BSC or BSC alone in a Phase 3 trial. Patients had previously received platinum-based therapy after which relapse had occurred. In the intent-to-treat (ITT) population, the median OS was 6.9 months for vinflunine plus BSC vs 4.6 months for BSC alone. In multivariate Cox analysis, the addition of vinflunine was independently correlated with improved survival (hazard ratio [HR]: 0.719; 95% confidence interval [CI]: 0.570-0.906, P =0.0052).[28] However, the response rate with vinflunine is disappointing and it has not been formally compared with other commonly used agents such as taxanes.

The current "watch-and-wait" approach for the management of metastatic UC following response to first-line chemotherapy prior to initiation of second-line treatment has not proven to be effective because almost all patients eventually relapse. A multicenter Phase 2 study of sunitinib as maintenance therapy in patients with advanced UC was recently reported.[32] Although the study terminated prematurely due to low patient recruitment, it provided a different perspective on the treatment of this disease (ie, maintenance therapy following response to first-line chemotherapy in an attempt to improve the durability of the initial response). Very recently, Powles et al reported the results of a Phase 2/3 study of lapatinib as maintenance treatment after first-line chemotherapy in patients with HER1/HER2-positive UC.[33] Between 2007 and 2013, 455 patients were screened and 232 HER 1 or 2 positive patients randomized to lapatinib (n = 116) or placebo (n = 116). The median PFS, median OS, and objective response rate (ORR) for lapatinib vs. placebo were 4.6 months (95% CI: 2.8 – 5.4) vs. 5.3 months (95% CI: 3.0 – 5.9) (HR: 1.04 [95% CI: 0.79 – 1.39] p = 0.77); 12.6 months (95% CI: 9.5 – 16.2) vs. 11.9 months (95% CI: 10.6 – 15.8) (HR 0.98 [95% CI: 0.71 – 1.35] p = 0.89); and 13.8% vs. 7.8%, respectively (p = 0.14). Subset analysis of 1) HER1/HER2 3+ positive UC patients on immunohistochemistry (IHC), 2) HER1-positive UC patients, and 3) HER2-positive UC patients showed no significant benefit for lapatinib compared to placebo in median PFS (HR 0.94, 0.99, and 1.19 respectively; p >0.05 for each) or median OS (HR: 0.76, 0.92, and 1.03 respectively; p >0.05 each). In addition, a study evaluating vinflunine[34,35] as a maintenance UC treatment is currently ongoing.

1.2.3.2. Rationale for Immunotherapy for Maintenance Treatment of Urothelial Cancer

There is a strong rationale for considering immunotherapy in patients with advanced UC. Urologists led the way in the use of immunotherapy in cancer in 1976, having introduced the tuberculosis vaccine bacille Calmette-Guérin (BCG), which stimulates a robust immune response in most patients and has become the standard of care as locoregional therapy after

surgical resection of non-muscle-invasive disease.[36,37] Multiple immunotherapies including interferon (IFN)-α, interleukin (IL)-2, IL-12, and IL-10 have been investigated, either as adjuncts with BCG or as a solo replacement therapy.[38,39] Over the past 40 years, progress evaluating immunotherapy for bladder cancer has been slow. Subsequently, the PD-1/PD-L1 pathway has emerged as an important biological pathway in UC.[40,41,42] PD-1, an immunoinhibitory receptor of the CD28 family, plays an important role in tumor immune escape.[43,44] The PD-1/PD-L1 interaction inhibits T-lymphocyte activation, proliferation, survival, and effector functions during anti-cancer immune response. Several tumors, including UC, present with high rates of somatic mutations,[45,46,47] possibly enhancing the host immune system's ability to recognize tumor cells as foreign owing to an increased number of antigens and stimulate T-cell response.[48] However, these cancers may also elude immune surveillance and eradication through the expression of PD-L1 in the tumor microenvironment,[49] which then becomes an important target for anti-PD-L1 antibodies. Indeed, antibodies blocking PD-1 and PD-L1 have demonstrated significant and durable response in patients with advanced UC. In a Phase 1b study of anti-PD-1 mAb pembrolizumab in heavily pre-treated patients with advanced UC,[40] the ORR was 24% (10% CR) among 33 treated patients with median follow-up duration of 11 months (range 10-13). The responses observed were durable, ranging from 16 to 40+ weeks (median not reached), with several responses ongoing at the time of analysis.

Similarly, an anti-PD-L1 mAb, MPDL-3280A, recently demonstrated significant durable response in heavily pre-treated patients with UC.[41,42] Preliminary data presented at the ASCO 2014 Annual Meeting from a Phase 1 study of MPDL-3280A as second-line treatment of patients with PD-L1 positive UC demonstrated noteworthy activity in 20 evaluable patients with an ORR of 50%, including 1 CR and 9 partial response (PRs).[41] Durable responses were also demonstrated with this agent in heavily pre-treated patients with advanced stage UC,[41,42] with an ORR of 54% in 68 patients with PD-L1-positive tumors, with durable ongoing responses up to 30.3 weeks reported.[41] Updated data from these studies with MPDL-3280A and pembrolizumab in patients with recurrent or metastatic PD-L1-positive UC further indicated durable responses with promising PFS and OS in patients with PD-L1-positive tumors, local immune/inflammatory cells, or stroma. Among 85 patients (46 PD-L1 immunohistochemistry [IHC] 2/3 and 38 IHC 0/1) with UC who received MPDL-3280A, the ORR for PD-L1 IHC 2+/3+ UC patients was 46% (95% CI: 31-61%; 6 CRs, 15 PRs) and IHC 0/1+ UC patients was 16% (95% CI 6-31%; 6 PRs); median response durations not reached (IHC 2/3 0+ to 54+ weeks; IHC 0/1 4+ to 33+weeks). Median PFS for IHC 2+/3+ UC patients was 24 weeks (95% CI 12-NE) and for IHC 0/1+ UC patients was 8 weeks (95% CI 6-12).[50] Among 33 patients enrolled with ≥1% PD-L1-positive cells in tumor nests or a PD-L1-positive band in stroma by IHC to receive pembrolizumab, 28 had measurable disease at baseline. In these evaluable patients, the ORR was 25% (95% CI: 11-45), with 3 (11%) CR and 4 (14%) PR, with durations ranging from 16 to 50+ weeks (median not reached at time of analysis).[51]

Avelumab, a potent and highly selective fully human mAb of the Ig G1 isotype, targets and blocks PD-L1, the ligand for PD-1 and B7.1 receptors. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1 and B7.1, removing the suppressive effects of PD-L1 on anti-tumor CD8+ T-cells and resulting in restoration of the cytotoxic T-cell response.[19]

Avelumab has demonstrated an efficacy and safety profile similar to other PD-1/PD-L1 inhibitors.[19,52]

In the ongoing Phase 1 study EMR 100070-001, 53 patients were treated with avelumab doses of 1.0, 3.0, 10.0, and 20.0 mg/kg administered IV Q2W in the dose escalation phase. The 10 mg/kg dose level was selected for further study and a summary of pooled safety data from1738 patients treated at this dose level in studies EMR 100070-001 and EMR 100070-003 (N=1738) is available with a data cutoff date of 09 June 2016.[19] The most frequently reported (incidence >5%) treatment-related adverse events were fatigue (17.7%), infusion-related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

Updated data from a pooled analysis of 249 patients enrolled in two advanced UC expansion cohorts in study EMR 100070-001 was recently published.[75] Patients were included regardless of PD-L1 expression levels. The median age was 68 years and 124 (50%) patients received 2 or more prior treatments for advanced or metastatic disease. At the time of the analysis (09 June 2016 data cut-off), the median followup was 9.9 months (range 4.3-12.1 months) and 60 (24%) patients were still on treatment. Among 161 post-platinum patients with at least 6 months of follow-up, the ORR was 17% (95% CI: 11-24%), including 9 CRs and 18 PRs. The disease control rate (DCR) was 40%, including 37 patients who had SD as their best response. An analysis using a cut-off of ≥5% for the expression of PD-L1 on tumor cells in 139 evaluable patients showed a 24% (15/63) ORR in the PD-L1 positive population and 13% (10/76) in the PD-L1 negative population, supporting that avelumab has anti-tumor activity in both the PD-L1 positive and negative populations. The median PFS was 11.9 weeks (95% CI: 6.1-18.0 weeks) and 6.1 weeks (95% CI: 5.9-8.0 weeks) in the PD-L1 positive and negative populations, respectively. The median OS was 8.2 months (95% CI: 5.7-13.7 months) and 6.2 months (95% CI: 4.3-14.0 months) in patients with PD-L1 positive and negative tumors, respectively.

These data support further evaluation of avelumab (MSB0010718C) for the treatment of patients with advanced stage UC. Given the poor prognosis for patients with advanced UC whose disease progresses after first-line chemotherapy, where patient outcomes are ultimately very poor,[30,53] a maintenance treatment with avelumab after first-line platinum-based chemotherapy may provide additional clinical benefit compared to the current watch-and-wait standard of care after chemotherapy. The current treatment recommendation for the first-line treatment of advanced UC is platinum-based chemotherapy,[1] which has been administered for a maximum of 6 cycles in previously completed clinical trials.[12,14,15,54] Due to the toxicities associated with platinum-based chemotherapy, these therapies are not administered long term; patients who respond to first-line treatment are then managed with BSC until disease relapse or progression, when second-line treatments are considered. The safety and efficacy of avelumab plus best supportive care (BSC, Arm A) and BSC alone (Arm B) will be evaluated in two coprimary populations: 1) patients with PD-L1-positive tumors (including infiltrating immune cells) confirmed by a verified Good Manufacturing Practice (GMP) PD-L1 IHC test, and 2) all randomized patients to assess the effects of avelumab in this therapeutic setting.

1.2.3.3. Rationale for Study Design

As described in the previous section, recent data demonstrate that immune checkpoint inhibitors, including avelumab, are capable of inducing objective tumor response in advanced UC patients and may provide further clinical benefit by prolonging overall survival.[41,42,51,55] The strategy of the proposed trial is to maintain or extend early clinical benefit following completion of first-line platinum-based chemotherapy in patients with advanced urothelial cancer by providing maintenance immunotherapy with avelumab. In this study, patients assigned to receive avelumab may continue to do so until their disease progresses or they discontinue due to other reasons. The potential benefits of avelumab maintenance therapy may include delay in the subsequent treatment with more toxic 2nd line chemotherapy as well as an improvement in overall survival.

An open-label design was chosen over a double-blind placebo-controlled design after assessment of risk-benefit considerations. As the study medication (avelumab) is administered as a 1-hour infusion, the use of an intravenous placebo would be associated with some risks (eg, injection site reactions) and with no benefit to the patient. Additionally, in order to preserve the blind, the use of a placebo infusion would require premedication with an H1 blocker and paracetamol prior to infusion as required for patients receiving avelumab to limit the incidence and severity of infusion-related reactions, an unnecessary practice for patients receiving placebo.

Overall survival (OS) will be the primary endpoint. PFS assessed by Blinded Independent Central Review (BICR) as well as the objective response as determined by RECIST v1.1 guidelines, will be secondary endpoints.

At the pre-specified interim analysis (Section 9.6), this study met the primary objective and demonstrated that avelumab plus BSC significantly prolongs OS compared to BSC alone in both co-primary populations (ie, in all randomized patients and in patients with PD-L1-positive tumors). Based on this result, the E-DMC recommended that remaining patients on Arm B who are progression-free be offered crossover to avelumab. For additional information, please refer to Supplement 1.

As the primary objective for the study was met (see above), a final OS update will be conducted after the target number of OS events has been reached (see Section 9.1; 425 OS events in all patients and 219 OS events in patients with PD-L1 positive tumors). Following this final OS update or approval of Protocol Amendment 6, whichever is later, the frequency of study procedures will be reduced for patients actively receiving avelumab and study participation for all others will be ended. Investigators will be appropriately notified once the final OS update has been completed and Amendment 6 can be fully implemented.

1.2.4. Rationale for Avelumab Dose and Best Supportive Care Regimens

Arm A patients will receive avelumab plus BSC. The avelumab dose will be 10 mg/kg administered as a 1-hour IV infusion every 2 weeks (Q2W). This dose is the recommended dose administered to >700 patients in the ongoing dose-expansion phase of study EMR 100070-001 (see Section 1.2.2.1 for details and the Avelumab Investigator's Brochure).[19]

Arm B patients will receive BSC as deemed appropriate by the treating physician (see Section 5.8). Currently, there are no approved therapeutic agents for the maintenance treatment of patients with unresectable UC who have completed prior systemic platinum-based therapy without progression of disease. Despite improvement of patient outcomes with these first-line therapies, durable and complete responses in patients with advanced UC are uncommon, and severe side effects limit long-term use of these agents. These patients are typically managed with BSC alone until progression of disease occurs, and only then are they treated with an alternate therapy.[13,30] Salvage cytotoxic agents have not demonstrated meaningful improvements in survival.[30] Initiation of maintenance therapy in an attempt to improve the durability of response and prolong time to progression is an alternate approach to management of this disease.[32,34,35,56] The "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4, Dec 2012) indicates that BSC may be an acceptable comparator in cases where there is no well-documented reference regimen.

1.3. Summary of Benefit-Risk Assessment

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

For single-agent avelumab, based on the nonclinical and Phase 1 trial EMR 100070-001 clinical data available to date, the conduct of the trial with the proposed avelumab dosing regimen is considered justifiable.

The anti-tumor activity of several PD-1/PD-L1 inhibitors,[40,41,42] including avelumab in the cohort of pretreated patients with UC in Study EMR 100070-001, support the formal testing of avelumab in the maintenance treatment setting following first-line chemotherapy in patients with unresectable locally advanced or metastatic UC that did not progress on first-line chemotherapy.

Available adverse event and laboratory abnormality data from patients with advanced solid tumors treated with single agent avelumab suggest an acceptable safety profile for this agent. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis (see Section 1.2.2.1).

Infusion-related reactions (including hypersensitivity) and immune related adverse events (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 a treatment algorithm and guidelines for treatment interruption and discontinuation in case of irAEs, as well as instructions for mandatory pre-medication with a histamine H1 receptor (H1) blocker and acetaminophen before the first 4 avelumab infusions.

Thus, the projected benefit/risk of avelumab administered in the first-line maintenance setting in patients with locally advanced or metastatic UC is anticipated to be favorable for investigation in this advanced cancer patient population.

Patients assigned to Arm B (BSC alone) who are progression-free and have not yet completed the EOT visit will be offered treatment with avelumab plus BSC maintenance therapy. For additional information, please refer to Supplement 1.

Of note, the benefit of avelumab plus BSC compared to BSC alone was demonstrated in a study population who had completed first-line chemotherapy 4-10 weeks prior to randomization to study treatment. The potential benefit of avelumab plus BSC is unknown for those in Arm B who might crossover to avelumab.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective

To demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging overall survival (OS) in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary UC patient population: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

Secondary Objectives

- To compare the PFS of avelumab plus BSC vs. BSC alone in patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and in all randomized patients.
- To evaluate the anti-tumor activity of avelumab plus BSC and BSC alone according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and in all randomized patients.
- To evaluate the overall safety profile of avelumab plus BSC and BSC alone.
- To evaluate the PK of avelumab in each of the co-primary UC patient populations treated with avelumab.
- To assess the immunogenicity of avelumab in each of the co-primary UC patient populations treated with avelumab.
- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in pre-treatment tumor tissue in each of the co-primary UC patient populations treated with avelumab.
- To evaluate the effect of avelumab plus BSC and BSC alone on patient-reported outcomes (PROs) in each of the co-primary UC patient populations.

Exploratory Objectives

- To explore the predictive and/or pharmacodynamic (PD) characteristics of peripheral blood and additional tumor tissue biomarkers relevant to the mechanism of action of or resistance to avelumab.

2.2. Endpoints

Primary Endpoint

- Overall Survival (OS).

Secondary Endpoints

- Progression-free survival (PFS) based on BICR assessment per RECIST v1.1.
- Investigator-assessed Progression-Free Survival (PFS). Objective Response (OR), Time to Tumor Response (TTR), Duration of Response (DR), and Disease Control (DC), as assessed per RECIST v1.1 by BICR and investigator.
- *Safety:* Adverse events (AEs) and laboratory abnormalities as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03; vital signs (blood pressure, pulse rate).
- *Pharmacokinetics (PK)*: maximum concentrations (C_{max}) and trough concentrations (C_{trough}) for avelumab.
- *Immunogenicity:* Anti-drug antibodies (ADA; neutralizing antibody [Nab]) against avelumab.
- *Biomarkers*: Tumor tissue biomarkers including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T lymphocytes.
- *Patient-Reported Outcomes:* patient-reported bladder cancer symptom, functioning, global quality of life (QOL), and Time to Deterioration (TTD) using the NCCN-FACT FBlSI-18; and health status using the EQ-5D-5L.

Exploratory Endpoints

- *Biomarkers:* Peripheral blood and additional tumor tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to anti-tumor immune response and/or response to or disease progression on avelumab, such as genes related to IFN-γ or transforming growth factor (TGF)-β.

3. STUDY DESIGN

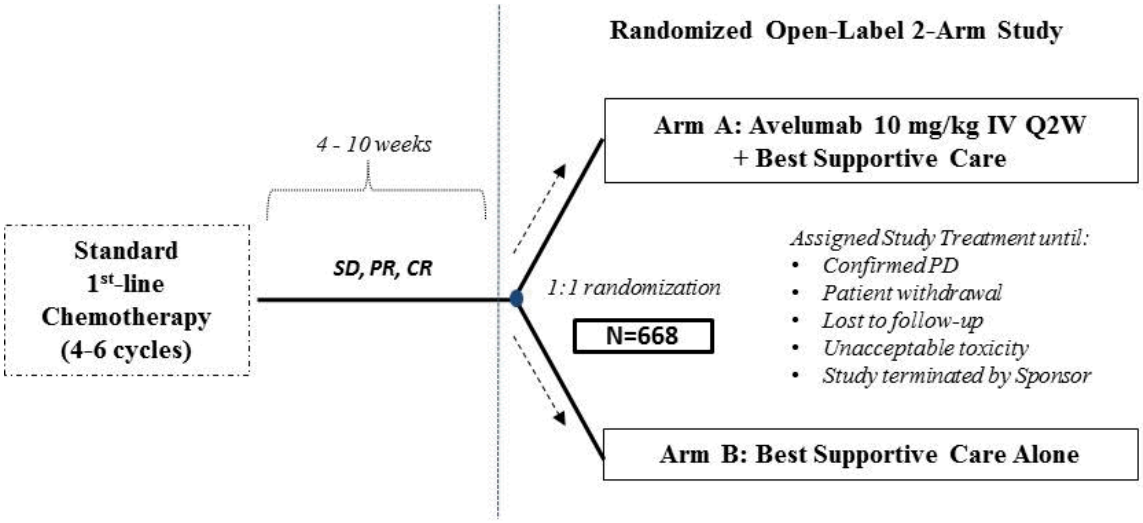
3.1. Study Overview

This is a Phase 3, multicenter, multinational, randomized, open-label, parallel-arm efficacy and safety study of avelumab plus BSC compared to BSC alone as a maintenance treatment

after completion of first-line platinum-based chemotherapy without evidence of disease progression in adult patients with unresectable locally advanced or metastatic UC.

The study design is illustrated in the following figure.

Figure 1 Study B9991001 Design



a. Allowed first-line chemotherapy regimens are gemcitabine + cisplatin or gemcitabine + carboplatin.
b. Randomization must occur at least 4 and not more than 10 weeks after the last dose of first-line chemotherapy and will be stratified by: best response on 1st-line therapy (CR or PR vs. SD) and metastatic disease site (visceral vs. non-visceral).

CR = complete response; IV = intravenous; PD = progressive disease; PR = partial response; Q2W = every 2 weeks; SD = stable disease

- Patients may sign informed consent at any time during or after completion of chemotherapy and prior to any study specific procedures, however must meet all eligibility requirements to be randomized in the study.

- A total of approximately 668 patients without progressive disease as per RECIST v1.1 guidelines (ie, with ongoing CR, PR, or SD) after 1st line chemotherapy will be allowed to be randomized in this study. It is estimated that at least 334 patients with confirmed PD-L1-positive tumors (including infiltrating immune cells) will be randomized in this study.

- Patients will be randomized in a 1:1 ratio into two study arms: avelumab plus BSC (Arm A) or BSC alone (Arm B).

- Patients must have received at least 4 cycles, but not more than 6 cycles of a first-line chemotherapy regimen consisting of either gemcitabine + cisplatin or gemcitabine + carboplatin before randomization into this study. No other chemotherapy regimen is allowed as the first line chemotherapy for inclusion in this clinical trial (please see Section 4.1, Inclusion Criterion #2).

- Randomization must occur at least 4 but not more than 10 weeks after the date of administration of the last dose of chemotherapy. Patients will initiate study treatment (Cycle 1 Day 1) within 3 days after randomization.

- Only patients without progressive disease as per RECIST v1.1 guidelines (ie, with ongoing CR, PR, or SD) after 4-6 cycles of chemotherapy will be allowed to be randomized in this study.

    - Post-chemotherapy confirmatory scan(s) (CT/MRI) for eligibility must be performed within 28 days prior to the date of randomization to assess response status following first-line chemotherapy.

    - Based on the post-chemotherapy confirmatory scan(s), the investigator should assess patient eligibility (ie, CR, PR, or SD) before randomization.

- This study is designed with two co-primary populations: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

- Randomization will be stratified by (i) best response to first-line chemotherapy (CR/PR vs. SD), and (ii) metastatic disease site (visceral vs. non-visceral) at the time of initiating first-line chemotherapy.

- Radiological tumor assessments will be conducted during the study at baseline as the post-chemotherapy confirmatory scan (as described above, within 28 days prior to randomization), at 8 weeks after randomization, then every 8 (±3 days) weeks for up to 1 year from randomization, and every 12 (±3 days) weeks thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Please see Section 3.1.2, Tumor Assessments for additional information.

- All patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first, regardless of initiation of anti-new cancer therapy(ies). Long-term follow-up survival assessments (every 3 months) may be completed at the investigative site or by telephone contact.

- Upon approval of protocol Amendment 5, patients assigned to Arm B (BSC alone) who are progression-free and have not yet completed the EOT visit will be offered treatment with avelumab plus BSC maintenance therapy. For additional information, including Schedule of Activities for those patients who crossover to avelumab, please refer to Supplement 1.

- Arm B patients who do not crossover to avelumab plus BSC will continue assessments as per protocol.

- As per Protocol Amendment 6, following the final OS update, the frequency of study procedures will be reduced while providing continued treatment for patients actively receiving avelumab and ending study participation for all patients who are not actively receiving avelumab (ie, Arm A patients in long-term follow-up and all Arm B patients who have not crossed over to receive avelumab).

3.1.1. Study Treatment

- For the purpose of this study, "study treatment" refers to both the investigational product (avelumab) plus BSC and BSC alone administered to patients during participation in this study.

- Study treatments may continue until confirmed disease progression as assessed by BICR, patient refusal, patient lost to follow up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Patient Withdrawal).

- According to the opinion of an investigator, if a patient in Arm A is still experiencing clinical benefit at the time of confirmed disease progression, the patient will be eligible for continued treatment with avelumab plus BSC, provided the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.4.1 Treatment after Initial Evidence of Radiologic Disease Progression). Radiological tumor assessments will be continued in these patients as described in the Section 3.1.2, Tumor Assessments.

- If a patient starts a new anti-cancer therapy before documented disease progression, then tumor assessments should be continued per the Schedule of Activities (unless not feasible) until documentation of disease progression or death, whichever occurs first.

- After review of radiologic images by BICR is stopped as per Protocol Amendment 6, following the final OS update, study treatment may continue until disease progression is assessed by the investigator, patient refusal, patient lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.5 Patient Withdrawal).

- **Arm A: Avelumab (MSB0010718C) plus Best Supportive Care**

  Patients randomized to avelumab plus BSC (Arm A) will be administered avelumab as a 1-hour IV infusion at a dose of 10 mg/kg once every 2 weeks together with BSC (see below).

  To mitigate potential infusion-related reactions, patients in Arm A will be premedicated prior to avelumab administration as described in Section 5.4.3.1. If an infusion-related reaction is observed, the infusion rate should be decreased or stopped depending on the severity of the event; please refer to Section 5.4.3.2 for further guidance.

- **Arm B: Best Supportive Care Alone**

  Patients randomized to BSC alone (Arm B) will be cared for as deemed appropriate by the treating physician. This could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC does not include any active anti-tumor therapy (see Section 5.8), however local radiotherapy of isolated lesions with palliative intent is acceptable as described in Section 5.9.2.

3.1.2. Tumor Assessments

Anti-tumor activity will be assessed by radiological tumor assessments and will be based on RECIST v1.1 (Appendix 2).

Tumor assessments will include all known or suspected disease sites. For all patients, imaging assessments will include chest, abdomen, and pelvis computerized tomography (CT) or magnetic resonance imaging (MRI) scans. Bone imaging, eg, bone scans or other methods considered standard of care locally, such as 18-Fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET) or MRI, are required at baseline (28 day screening period). (**Note**: ^{18}FDG-PET may not be a permissible alternate for bone imaging at some centers or countries (eg, investigative sites in Canada). Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone imaging will only be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of complete response (CR) confirmation, and at every other tumor assessment visit (ie, every 16 weeks for the first year after randomization and every 24 weeks thereafter) if considered local standard of care.

Brain imaging (eg, MRI) is required at baseline for patients who have a history of brain metastases or for whom brain metastases are suspected during screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases at baseline; otherwise brain will only be evaluated when clinically indicated.

Both pre-chemotherapy and post-chemotherapy scans must have been performed and be readily available during screening. Post-chemotherapy confirmatory scan for eligibility must be performed within 28 days prior to the date of randomization to assess response status following first-line chemotherapy. This scan will also be used as the baseline scan for the tumor assessments in this study.

For all patients, radiological tumor assessments (including chest, abdomen, and pelvic CT or MRI scans) will be conducted at baseline (ie, the post-chemotherapy confirmatory scan within 28 days prior to randomization), at 8 weeks after randomization, then every 8 (±3 days) weeks for up to 1 year from randomization, and every 12 (±3 days) weeks thereafter until documented disease progression as assessed by BICR regardless of initiation

of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. In the absence of clinical deterioration, patients with PD should remain on the current study treatment until PD is confirmed by BICR. Further details regarding tumor assessments are provided in Section 7.7.

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

All radiographic images from the time of the most recent tumor assessment prior to first-line chemotherapy until documented disease progression will be submitted to an independent third-party core imaging laboratory for Blinded Independent Central Review (BICR) as described in the Study Manual.

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

As per Protocol Amendment 6, following the final OS update, tumor assessments will be performed by the study investigator at a frequency as per local standard of care and when progression is suspected. Radiologic images will no longer be submitted for independent central review or entered into the CRF.

3.1.3. Safety Assessment

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

3.1.4. Patient-Reported Outcomes

PROs will be assessed using 2 published and validated instruments, NCCN-FACT FBlSI-18 and EQ-5D-5L.

In the treatment of UC, delay of worsening of symptoms and maintenance of QOL is a treatment goal with the currently available non-curative therapies.[57] To that end, Herman et al, (2004)[58] demonstrated that the combination of gemcitabine with radiation therapy maintained overall QOL versus radiation alone, as indicated by the FACT-Bl. The NCCN-FACT FBlSI-18 (a later version of the FACT-Bl) was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system[59,60] and was specifically created with input from the Food and Drug Administration (FDA) and validated in bladder cancer patients.[61] The NCCN-FACT FBlSI-18 is designed to be a stand-alone instrument to measure symptoms and QoL in patients with UC and was created using inputs from patients and oncologists.[62] The 'Disease Related Symptoms-Physical' subscale of the NCCN-FACT FBlSI-18 (FBlSI-DRS-P), uses a subset of physical symptoms which are considered to be specific to UC.[61]

The EuroQol EQ-5D-5L is a 6-item patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[63] There are 2 components to the EuroQol EQ-5D-5L, a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.[64] Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction.

3.1.5. Pharmacokinetic/Immunogenicity Assessments

Sparse plasma/serum PK/immunogenicity sampling will be collected for avelumab and anti-drug antibodies (ADA). Sampling will only be done in patients randomized to Arm A. Refer to the Schedule of Activities table and Sections 7.3 and 7.4 for additional details of the PK and immunogenicity collections.

3.1.6. Biomarker Assessments

Mandatory baseline (recent) tumor tissue, as well as archival tumor tissue, if available, will be collected from all patients to support investigation and, as appropriate, clinical validation of biomarkers that may predict response to treatment. End of Treatment tumor tissue from a *de novo* biopsy should also be obtained unless clinically contraindicated to support an investigation of mechanisms of resistance. Banked blood biospecimen will be collected from all patients at baseline, on treatment and at End of Treatment/Withdrawal to support exploratory investigation of possible markers predictive of clinical benefit, pharmacodynamic markers and/or markers of intrinsic or acquired resistance.

Biomarker assessments are described in the Schedule of Activities table and in Section 7.5 and Section 7.6.

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Diagnosis:

    a. Histologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium.

    b. Documented Stage IV disease (per American Joint Committee on Cancer/International Union for Cancer Control Tumor Node Metastasis (TNM) system, 7th edition)[65] at the start of first-line chemotherapy.

    c. Measurable disease prior to the start of first-line chemotherapy by RECIST v1.1.

2. Prior first-line chemotherapy must have consisted of at least 4 cycles and no more than 6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin. No other chemotherapy regimens are allowed in this study.

    a. The last dose of first-line chemotherapy must have been received no less than 4 weeks, and no more than 10 weeks, prior to randomization in the present study.

3. Patients without progressive disease as per RECIST v1.1 guidelines (ie, with an ongoing CR, PR, or SD) following completion of 4 to 6 cycles of first-line chemotherapy.

    a. Eligibility based on this criterion will be determined by investigator review of pre-chemotherapy and post-chemotherapy radiological assessments (CT/MRI scans); see Study Overview, Section 3.1.

4. Provision of a recent formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (or subsection thereof) from the most recent primary or metastatic tumor biopsy or resection obtained prior to treatment with first line chemotherapy but within 24 months prior to randomization, with no intervening systemic anti-cancer therapy. If a FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable.

    If a suitable tissue sample is not otherwise available, then a *de novo* biopsy (core needle or excisional) must have been obtained for research purposes prior to randomization in this study.

    Note: tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or bone metastases are not acceptable and should not be submitted.

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

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

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

8. Estimated life expectancy of at least 3 months.

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

10. Adequate bone marrow function, including:

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

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

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

11. Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation (Appendix 4) or by 24-hour urine collection for creatinine clearance or according to the local institutional standard method.

12. Adequate liver function, including:

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

    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5 × ULN.

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

14. Female patients of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception (Section 4.3.1) throughout the study and for at least 30 days after the last dose of assigned treatment.

4.2. Exclusion Criteria

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

1. Patients whose disease progressed by RECIST v1.1 on or after first-line chemotherapy for urothelial cancer.

2. Prior adjuvant or neoadjuvant systemic therapy within 12 months of randomization.

3. Prior immunotherapy with IL-2, IFN-α, or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or CTLA-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

4. Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomization. Prior palliative radiotherapy is permitted, provided it has been completed at least 48 hours prior to patient randomization.

5. Patients with known symptomatic central nervous system (CNS) metastases requiring steroids. Patients with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to randomization, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.

6. Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1; however, alopecia, sensory neuropathy Grade ≤2 is acceptable, or other Grade ≤2 adverse events not constituting a safety risk based on the investigator's judgment are acceptable.

7. Diagnosis of any other malignancy within 5 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, low-grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration), or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms.

8. Participation in other studies involving investigational drug(s) within 4 weeks prior to randomization. Observational studies are permitted.

9. 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.

10. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

11. Active infection requiring systemic therapy.

12. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3), any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of asthma symptom control per the Global Initiative for Asthma 2015).[66]

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

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

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

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

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

15. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy.

16. Positive test for human immunodeficiency virus (HIV) infection or known acquired immunodeficiency syndrome (AIDS).

17. 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).

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

19. Patients who are investigational 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 directly involved in the conduct of the study.

20. Pregnant female patients; breastfeeding female patients; and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol for the duration of the study and for at least 30 days after the last dose of investigational product.

21. Other severe acute or chronic medical conditions including but not limited to colitis, inflammatory bowel disease, pneumonitis, and pulmonary fibrosis; 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 study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4.3. Lifestyle Guidelines

4.3.1. Contraception

Contraception use and pregnancy test will be evaluated in all patients at screening prior to randomization. However, following assignment to treatment only patients assigned to Arm A (avelumab plus BSC) will be required to remain on contraception as described below.

In Arm A of this study, female patients who are of childbearing potential will receive avelumab for which the teratogenic risk is currently unknown.

All female patients of childbearing potential who are, in the opinion of the Investigator, sexually active and at risk for pregnancy must agree to use a highly effective contraception method, preferably with low user dependency, during treatment and for at least 30 days after the last dose. The investigator or his or her designee, in consultation with the patient, will select an appropriate method of contraception for the individual patient from the list of permitted contraception methods (see below), and instruct the patient in its consistent and correct use.

Patients need to affirm that they meet the criteria for the correct use of the selected method of contraception. At time points indicated in the Schedule of Activities, the investigator or his or her designee will discuss with the patient the need to use the selected contraception method consistently and correctly and document such conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or to the male patient's partner.

Contraception Methods

Highly Effective Methods of Contraception That Have Low User Dependence include the following:

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

2. Intrauterine device (IUD).

3. Intra-uterine hormone-releasing system (IUS).

4. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the male partner is the sole sexual partner of the female of child-bearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

5. Bilateral tubal occlusion.

Highly Effective Methods of Contraception That Are User Dependent include the following:

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

    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;
    - Injectable.

3. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.

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

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as 60 years or older or no cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause. Status may be confirmed by having a serum follicle-stimulating hormone (FSH) level test.

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

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Manual.

To facilitate access to appropriately-qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains,

at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and 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 investigational site.

5. STUDY TREATMENTS

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

For the purpose of this study, the investigational product is avelumab (MSB0010718C).

For the purpose of this study, "study treatment" refers to both the investigational product (avelumab) plus BSC and BSC alone administered to patients during participation in this study. Please see Section 5.8 for additional information regarding BSC.

5.1. Allocation to Treatment

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

Qualified patients who have signed an Informed Consent Form and meet all eligibility criteria will be randomized in a 1:1 ratio to receive avelumab plus BSC (Arm A) or BSC alone (Arm B). Allocation of patients will be stratified according to best response to first-line chemotherapy (CR/PR vs. SD) and site of metastases (visceral vs. non-visceral) at the time of initiating first-line chemotherapy. The "non-visceral" stratum includes patients with locally-advanced disease as well as patients with only non-visceral disease. This stratified randomization will be centrally allocated across all centers using an Interactive Response Technology (IRT) system (an interactive web-based response system).

The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, patient identifiers and demographic information, and stratification factors. The site personnel will then be provided with a treatment assignment. The IRT system will also provide a confirmation report containing the patient number; this confirmation report must be stored in the site's files.

Study treatment (Cycle 1 Day 1) must start within 3 days after patient randomization.

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

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

Arm B patients who crossover to receive avelumab plus BSC will be assigned avelumab in the IRT system according to instructions provided by the Sponsor.

5.2. Patient Compliance with Avelumab Study Treatment

All doses of investigational product will be administered by the appropriately designated study staff at the investigational site.

5.3. Investigational Product Supplies

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

5.3.1. Avelumab Dosage Form(s) and Packaging

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

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

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

5.3.2. Avelumab Preparation and Dispensing

See the Dosage and Administration Instructions (DAI), which is located in the Investigational Product 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, national, and institutional guidance.

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 anticancer agents.

Avelumab will be administered 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 administration in this trial, avelumab drug product must be diluted with 0.9% sodium chloride (normal saline). 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 DAI. During avelumab administration, tubing with in-line, low protein binding 0.2 micron filter made with polyether sulfone (PES) must be used.

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.

5.4. Avelumab Administration

Avelumab will be administered at the investigational site on an outpatient basis as detailed in the DAI.

Avelumab will be administered at 10 mg/kg on Day 1 and Day 15 of each 4-week treatment cycle after all procedures/assessments have been completed as described in the Schedule of Activities table. All safety assessments must be performed, and results reviewed by the treating physician prior to study treatment administration.

Avelumab will be administered as a 1-hour IV infusion. In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids. Sites should make every effort to target infusion timing to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of -10 minutes and +20 minutes is permitted (ie, infusion time is 60 minutes: -10 min/+20 min). The exact duration of infusion should be recorded in both source documents and case report forms (CRFs).

Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.4.3.2.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for every dose. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug required for preparation and administration for the current dose must be recalculated using this most recent weight obtained. For weight change less than 10%, the decision to recalculate the avelumab dose can be in accordance with institutional practice. Avelumab dose reduction for toxicity management is not permitted, however the next dose administration may be omitted due to persisting toxicity as described in Table 3 and Section 5.4.3.

5.4.1. 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. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If radiologic imaging shows disease progression as assessed by BICR (or as assessed by Investigator as per Protocol Amendment 6, following the final OS update), after discussion between the Sponsor and Investigator, patients may continue to receive avelumab at the Investigator's discretion if the following criteria are met:

- 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.

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

As per Protocol Amendment 6, following the final OS update, patients who stop avelumab treatment and subsequently experience radiologic disease progression, will no longer be eligible for re-treatment with avelumab.

5.4.2. Food Requirements

Avelumab may be administered without regard for food.

5.4.3. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule.

For avelumab, no dose modifications are permitted in this study, but next infusion may be omitted based on persisting toxicity. Recommended toxicity management guidelines with regard to avelumab infusion omissions are shown in Table 3.

Table 3. Avelumab Infusion Omissions for Avelumab Product-Related Toxicity

Toxicity	NCI CTCAE Severity Grade	Avelumab Treatment Modification
Infusion-related Reaction / Hypersensitivity	Grade 1-4	• See Section 5.4.3.2 and Table 4.
Tumor lysis syndrome	Grade 1-4	• See Section 5.4.3.3 and Figure 2.
Immune-related AE (irAE)	Grade 1-4	• See Section 5.4.3.4 and Table 5.
Drug-related adverse reactions (excluding infusion-related reaction / hypersensitivity and immune-related AE)	Grade 1	• Continue as per schedule.
	Grade 2	• Continue as per schedule.
	Grade 3	• Withhold until recovery to Grade ≤1 or baseline. • Permanently discontinue if toxicities do not resolve to Grade ≤1 or baseline within 12 weeks of last administration or if the same Grade 3 toxicity recurs. Exceptions are: • Laboratory values out of normal range that do not have any clinical correlate.
	Grade 4	• Permanently discontinue. **Exceptions are:** • Laboratory values out of normal range that do not have any clinical correlate.

Avelumab infusion-related reactions (including hypersensitivity) and irAEs should be handled according to guidelines in Section 5.4.3.2 Management of Avelumab Infusion-Related Reactions and Section 5.4.3.4 Management of Avelumab Immune-Related Adverse Events.

5.4.3.1. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be

administered for subsequent avelumab doses based upon clinical judgement and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids.

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

Infusion of avelumab will be stopped in case of Grade ≥2 infusion-related, allergic, or anaphylactic reactions. Symptoms of avelumab infusion related reactions include, but are not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of avelumab infusion related reactions is described in Section 5.4.3.2. Patients should be instructed to immediately report to the Investigator any delayed reactions that may occur after they leave the clinic.

5.4.3.2. Management of Avelumab Infusion-Related Reactions/Hypersensitivity Reactions

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 4.

Table 4. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

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

Table 4. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modification for Avelumab
• Grade 4: Life-threatening consequences; urgent intervention indicated.	

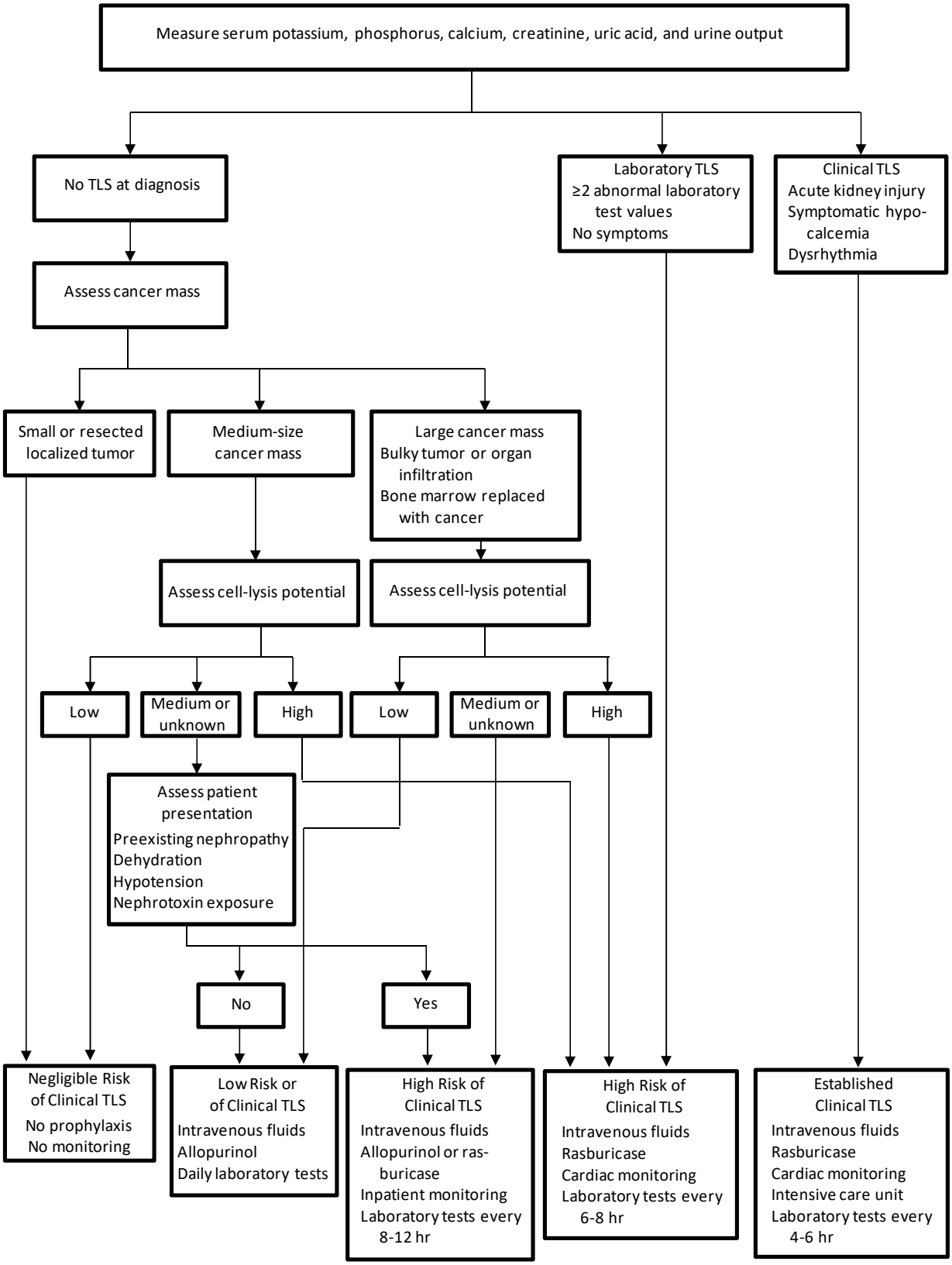
IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs.
*If the avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, at the Investigator's discretion, 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 4 (including reducing the infusion rate by 50%), the investigator may consider treatment with corticosteroids, and the infusion should not be resumed for that dose. At the next dose, the investigator may consider the addition of H2-blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.4.3.3. Management of Avelumab-Related Tumor Lysis Syndrome

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumor lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 2) published by Howard et al.[67]

Figure 2 Assessment and Initial Management of Tumor Lysis Syndrome (TLS)



5.4.3.4. Management of Avelumab Immune-Related Adverse Events

Treatment of irAEs should follow guidelines set forth in Table 5.

Table 5. 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 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Table 5. Management of Avelumab Immune-Related Adverse Events

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 Grade 2 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.	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

Table 5. Management of Avelumab Immune-Related Adverse Events

	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.	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.	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

Table 5. Management of Avelumab Immune-Related Adverse Events

	Consult gastroenterologist/hepatologist. Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	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.	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

Table 5. Management of Avelumab Immune-Related Adverse Events

	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.	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. European Society of Cardiology or American Heart Association guidelines European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines. American Heart Association 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	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and

Table 5. Management of Avelumab Immune-Related Adverse Events

	hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone): • 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.

Table 5. Management of Avelumab Immune-Related Adverse Events

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: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; ULN=upper limit of normal.

5.5. Investigational Product Storage

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

Investigational product should be stored in its original container and in accordance with the label. See the DAI for storage conditions for avelumab once reconstituted and/or diluted.

Avelumab must be stored in the refrigerator at 2 – 8 °C (36 – 46 °F). Do not freeze. Protect from light. Do not shake vigorously.

Storage conditions stated in the SRSD (ie, Avelumab Investigator's Brochure) will be superseded by the storage conditions stated on the label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). Storage temperatures must be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, must be regularly inspected to ensure it is maintained in working order.

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

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

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

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the label are not considered excursions. More specific details will be provided to the sites separately.

All study drug supplies must be kept in a locked, limited access room. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the sponsor. The investigator and or site staff must report any unacceptable condition of the investigational product to the site monitor.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. The sponsor will provide instructions as to disposition of any unused investigational product if the investigative site is unable to destroy at site per local procedures.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product-supplies.

Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities.

The prescribed dose must be recorded in the patient's medical records. Drug dispensing needs to be verified and documented by a second individual and the forms must be signed by both the individual who dispensed the drug and the second individual who verified the dispensing. Copies must be provided to Pfizer.

5.7. Destruction of Investigational Product Supplies

At the end of the trial, or at appropriate points during the trial, Pfizer or designee will provide instructions as to disposition of any unused investigational product. If Pfizer or designee authorizes destruction at the trial 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. All destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

5.8. Best Supportive Care

All patients will receive BSC during this study. BSC will be prescribed and/or administered per current treatment practices at each investigational site and per individual patient needs and could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including radiotherapy), etc. BSC does not include any active anti-tumor therapy; however, local radiotherapy of isolated lesions with palliative intent is acceptable as described in Section 5.9.2.

All BSC components must comply with the permitted medications described in this protocol (see Section 5.9).

5.9. Concomitant Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or

vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

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

Concomitant medications, blood products, non-drug interventions, and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment (Arm A) or 90 days after the End of Treatment (EOT) visit (Arm B).

All concomitant medications will be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis) and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). During study treatment, concomitant medications should be reviewed at each study visit, and any prohibited treatments should be discussed and appropriately managed.

Given that recording of non-serious AEs ends when a patient begins a new anti-cancer therapy (Section 8.2), recording of concomitant medications associated with these non-serious AEs should also end. However, given that SAEs must continue to be recorded up to 90 days after the last dose of study treatment(s) even if the patient begins a new anti-cancer therapy, concomitant medications associated with these SAEs must also be recorded.

As per Protocol Amendment 6, following the final OS update, concomitant medications/treatments will not be captured in the CRF unless they contribute to or are associated with the treatment for an AE.

Concurrent anticancer therapy with agents is not allowed, other than avelumab in patients randomized to Arm A. 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 flu-like symptoms, tumor lysis syndrome, and irAE are reported in Sections 5.4.3.2, 5.4.3.3, and 5.4.3.4, respectively.

5.9.1. Concomitant Surgery

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

In the case of a surgical procedure, avelumab treatment should be withheld. Postoperatively, the decision to reinitiate avelumab treatment should be discussed with the sponsor's medical monitor.

5.9.2. Concomitant Radiotherapy

Local radiotherapy of isolated lesions with palliative intent is acceptable (eg, bleeding, pain, compression), however all attempts should be made to rule out disease progression.

Palliative radiotherapy is permitted if considered medically necessary by the treating physician. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should also be present at baseline; otherwise, painful lesion(s) requiring radiotherapy will be considered as a sign of disease progression.

5.9.3. Other Prohibited Concomitant Medications and Therapies

All patients are prohibited from receiving the following therapies while receiving study treatment:

- Anti-cancer systemic chemotherapy or biological therapy or investigational agents other than avelumab.
- Other experimental pharmaceutical products.

Patients enrolled on Arm A are prohibited from receiving the following therapies while receiving study treatment:

- Immunotherapy, immunosuppressive drugs (ie, chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions or for the treatment of irAEs). Short term administration of systemic steroids (eg, for allergic reactions or the management of irAEs) is allowed. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection) are allowed.
- Any vaccine therapies for the prevention of infectious disease within 4 weeks of start of study treatment, except for inactivated vaccines (eg, influenza vaccine).
- Bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to receiving the first administration of avelumab.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion).
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).

Clarifications About Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[68,69] Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 agents indicate that short-term use of steroids may be employed without compromising clinical outcomes.[70] Therefore, the use of steroids during this trial is restricted as follows for patients receiving avelumab:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 5.

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

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

- 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.

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

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 5.

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

- 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 factor 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) table and Assessments section (Section 7).

6.1.1. Tumor Biospecimens

Provision of a tumor biospecimen will be required for randomization into the study as follows:

1. Recent tumor biospecimen: A mandatory FFPE tumor tissue block (or subsection thereof) must be obtained from all patients representing tumor tissue from the most recent primary or metastatic tumor biopsy or resection obtained prior to treatment with first line chemotherapy but within 24 months prior to randomization, with no intervening systemic anti-cancer therapy between the time the tissue was obtained and initiation of first-line chemotherapy. If an FFPE tissue block cannot be provided due to local regulation or policy, 15 freshly cut unstained slides (10 minimum) will be acceptable.

   Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or bone metastases is not adequate and should not be submitted. If a suitable tissue sample is not otherwise available, then an FFPE tissue sample from a *de novo* biopsy (core needle or excisional) must be obtained for research purposes during the screening period for this study (after informed consent has been obtained and prior to randomization).

   Note: This mandatory tumor tissue sample must be submitted to the Central Laboratory prior to randomization.

2. Archival tumor biospecimen: An archival FFPE tumor tissue block (or subsection thereof) collected at the time of primary diagnosis or first tumor resection (if different from the most recent sample described above) is strongly encouraged to assess changes in the tumor microenvironment relative to the most recent sample (per above). If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable. A sample from a later timepoint that is still prior to the most recent tumor tissue sample (per above) may be substituted, if necessary. Tumor tissue from cytologic samples (eg, FFPE cell pellet from Fine Needle Aspiration biopsy) or bone metastases are not acceptable.

End of Treatment Tumor Biospecimen: A *de novo* tumor sample (ie, fresh biopsy) should also be collected at End of Treatment unless clinically contraindicated. This *de novo* biopsy should be formalin-fixed and paraffin-embedded as per routine procedures (see Laboratory Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. If an FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable.

Please refer to Section 7.5.1 for planned analyses of tumor biospecimens. Additional information on tumor biospecimen collection procedures is included in the Laboratory Manual.

6.2. Treatment Period

For treatment period procedures, see Schedule of Activities table and Assessments section (Section 7). Patients who refuse to return to the site for evaluations should be contacted by telephone every 3 months as an alternative to site visits, as all patients will be followed for survival until death, end of the study, or patient withdrawal of consent, whichever comes first.

As per Protocol Amendment 6, following the final OS update, only patients receiving avelumab will continue in the treatment phase of this study. All Arm B patients who have not crossed over to receive avelumab and are still in the treatment phase will be discontinued. Please refer to the "Protocol Amendment 6: Schedule of Activities for Study Treatment, End of Treatment and Follow-up Periods" for study procedures to be performed for patients continuing to receive avelumab.

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

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

Beyond the 90 days until the end of the study (long-term follow-up), all patients will be followed every 3 months after the last study clinic visit (±14 days) for survival, tumor assessment, and new systemic anticancer treatment; additional timepoints to collect survival information may be requested by the Sponsor in preparation for interim and final analyses.

As per Protocol Amendment 6, following the final OS update, only patients who received avelumab will be followed through the 90-day Short-term Follow-up Visit. Patients who are receiving or have received BSC alone and are in the treatment or 90-day Short-term Follow-up phase will be discontinued with no further follow-up. No additional OS follow-up will be performed for any study patient.

6.4. End of the Study

The study will end when at least 425 and 219 OS events have occurred for all randomized patients and patients with PD-L1-positive tumors, respectively.

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

6.5. Patient Withdrawal

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

Reasons for withdrawal of study treatment may include:

- Confirmed disease progression as assessed by BICR (or as assessed by Investigator as per Protocol Amendment 6, following the final OS update). However, patients receiving avelumab with disease progression who are continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.4.1);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

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

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

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he or she has taken to ensure that normal processes are adhered to as soon as possible. The sponsor's study team will be informed of these incidents in a timely fashion.

7.1. Safety Assessment

Safety assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs, physical examination, laboratory assessments (including pregnancy tests), and verification of concomitant medications. Further details of these assessments are described in the Schedule of Activities.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on 2 occasions prior to starting study treatment: once at the start of screening, and once at the Cycle 1 Day 1 visit for Arm A patients immediately before the administration of study treatment. 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 Cycle 1 Day 1 visit before the patient may receive avelumab study treatment. For patients receiving avelumab study treatment, serum or urine pregnancy tests will also be routinely repeated as described in the Schedule of Activities tables and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive human chorionic gonadotropin (hCG) test, the patient will be withdrawn from treatment but may remain in the study.

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

As per Protocol Amendment 6, following the final OS update, negative pregnancy test results need not be recorded in the CRF.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by NCI CTCAE version 4.03, Appendix 3), timing, seriousness, and relatedness. Adverse events that occur during the study will be recorded on the adverse events CRF page.

7.1.3. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. Clinically significant abnormal laboratory test results should be

repeated as soon as possible (preferably within 24-48 hours). The required laboratory tests are listed in Table 6 and Table 7. As per Protocol Amendment 6, following the final OS update, laboratory test results need not be recorded in the CRF unless the findings support an AE.

Table 6. Prior to Protocol Amendment 6: Required Laboratory Tests

Hematology	Chemistry Panel (* denotes core chemistry test)	Urinalysis	Coagulation Tests	Pregnancy Tests
Hemoglobin	ALT*	Protein, glucose, blood	PT or INR	For female patients of childbearing potential, serum or urine
Platelets	AST*		PTT or aPTT	
WBC	Alkaline Phosphatase*			
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Total Calcium*			
	Total Bilirubin*[$]			
	BUN or Urea*			
	Creatinine*			
	Glucose*			
	Phosphorus or Phosphate*			
	Albumin			
	Total Protein			
	Uric Acid			
	Amylase			
	Gamma glutamyl transferase (GGT)			
	Cholesterol			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			
	Lipase			
	Triglycerides			
	HBV, HCV testing			
	HIV serology			
	Thyroid Function Tests: TSH, free T4			
	Cardiac biomarkers: Troponin (cTnT or cTnI)[†]			
	Other Tests: ACTH			

[$] For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, PT/INR, alkaline phosphatase.

† Measurement of cTnT is preferred; however, cTnI may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured during screening should be measured consistently throughout the study for any given patient.

ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, cTnI= cardiac troponin subunit I, cTnT= cardiac troponin subunit T, GGT=gamma-glutamyltransferase, HBV= hepatitis B

virus (eg, HBsAg, Hepatitis B core antibody), HCV=hepatitis C virus (eg, Hep C antibody), HIV=human immunodeficiency virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PT=prothrombin time, PTT=partial thromboplastin time, TSH=thyroid-stimulating hormone, WBC=white blood cell

Table 7. Protocol Amendment 6: Required Laboratory Tests

Hematology	Chemistry Panel	Pregnancy Tests
Hemoglobin	ALT	For female patients of childbearing potential, serum or urine
Platelets	AST	
WBC	ALP	
Absolute Neutrophils	Total Bilirubin°	
Absolute Lymphocytes	BUN or Urea	
	GGT	
	Amylase	
	Lipase	
	Creatinine	
	Potassium (if clinically indicated)	
	Sodium (if clinically indicated)	
	Total Calcium (if clinically indicated)	
	Creatine kinase	
	Glucose (non-fasted)	
	Thyroid Function Tests: Free T4, TSH	
	ACTH	

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

Abbreviations: ACTH=adrenocorticotropic hormone, ALP= alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, GGT=gamma-glutamyl transferase, INR=international normalized ratio, PT=prothrombin time, T4=thyroxine, TSH=thyroid-stimulating hormone, WBC=white blood cell.

7.1.4. Physical Examinations and Vital Signs

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

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

Vital signs (blood pressure and pulse rate) and weight will be measured on study days as described in the Schedule of Activities. Blood pressure and pulse rate should be taken prior to study drug dosing (if applicable) and with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

As per Protocol Amendment 6, following the final OS update, physical examinations, vital signs, and ECOG performance status need not be recorded in the CRF unless the findings support an AE. Clinically significant findings must be reported as AEs.

7.1.5. (12-Lead) Electrocardiograms

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

All patients require a single ECG measurement at screening (clinically significant abnormal findings in baseline ECGs will be recorded as medical history). On-treatment ECGs will be performed as clinically indicated.

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

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

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

As per Protocol Amendment 6, following the final OS update, ECG results need not be recorded in the CRF unless the findings support an AE.

7.2. Patient-Reported Outcome Assessments

The NCCN-FACT FBlSI-18 and EQ-5D-5L questionnaires will be administered at time points described in the Schedule of Activities. The amount of time for a patient to complete the questionnaire is estimated to be about 3-5 minutes.

As per Protocol Amendment 6, following the final OS update, Patient-Reported Outcome Assessments will no longer be performed/collected.

7.3. Pharmacokinetics Assessments

Blood samples (3.5 mL serum separator (SST) tube per timepoint) for PK analyses will be collected from Arm A patients as outlined in the Schedule of Activities table. Do not collect blood from the same arm being infused. Where noted in the Schedule of Activities, PK blood samples will be collected at approximately the same time as other assessments wherever possible.

For all PK blood sample collections, the actual time of avelumab dosing, as well as actual times of PK collections, will be recorded in the source document and CRF.

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

All efforts will be made to obtain the PK blood samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) will be considered protocol compliant, and the exact time of the sample collection noted on the CRF. If a scheduled PK blood sample collection cannot be completed for any reason, the missed sample collection may be rescheduled with agreement of the investigator and sponsor.

PK blood samples will be assayed for avelumab using validated analytical methods. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the study manual. As part of the understanding of the PK of the study drug, samples may be used for further evaluation of the bioanalytical methods for avelumab. The results of such analyses may be included in the clinical report.

As per Protocol Amendment 6, following the final OS update, the collection of PK blood samples will no longer be performed/collected.

7.4. Immunogenicity Assessment

Blood samples (3.5 mL SST tube per timepoint) for evaluation of avelumab immunogenicity will be collected from Arm A patients as outlined in the Schedule of Activities table. Immunogenicity blood samples will be assayed for anti avelumab antibodies using a validated analytical method. All samples should be drawn within 2 hours before the start of avelumab infusion. All of the samples that are positive for ADA may also undergo characterization for neutralizing antibodies. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

As per Protocol Amendment 6, following the final OS update, the collection of immunogenicity blood samples will no longer be performed/collected.

7.5. Translational and Pharmacodynamic Assessments

7.5.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

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

Tumor tissue biomarker status will be determined by analytically validated tests developed by the sponsor; tumor tissue biomarkers analyzed may include, but may not necessarily be limited to, PD-L1 expression and quantitation of tumor-infiltrating CD8+ T-lymphocytes by IHC. Optional tumor biopsies obtained at the End of Treatment/Withdrawal will be assessed

to the pre-treatment biopsies (archival or *de novo*) to investigate acquired mechanisms of resistance.

Only core needle or excisional biopsies, or resection specimen are suitable. Cytologic preparations, such as fine needle aspiration biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Study Manual.

7.5.2. Peripheral Blood

Specimens will be retained as banked biospecimens (see Section 7.6) and will include whole blood, serum and plasma samples that will be retained in a biobank for exploratory assessments, unless prohibited by local regulation or by decision of the Institutional Review Board or Ethics Committee. Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to study treatment. These include biomarkers that may aid in the identification of those patients who might preferentially benefit from treatment with avelumab plus BSC vs. BSC alone, including but not limited to biomarkers related to anti-tumor immune response or target modulation, such as soluble IL-8 or IFNγ, and/or tissue FoxP3, PD-1, PD-L2.

As per Protocol Amendment 6, following the final OS update, the collection of biomarkers will no longer be performed/collected.

7.6. Banked Biospecimens

7.6.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and patients, unless prohibited as such by local regulations or ethics committee decision.

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study ID number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be

stored indefinitely to allow for future research on the topics described here, including research conducted during the drug development process and also postmarketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which case any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

A single 4 mL blood biospecimen **Prep D1** (**K_2 edetic acid [ethylenediaminetetraacetic acid, EDTA] whole blood collection optimized for DNA analysis)** will be collected on or prior to the Cycle 1 Day 1 visit (prior to dosing for Arm A patients and at any time for Arm B patients) to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

Additional biospecimens to be retained for exploratory analyses in this study, as described in Section 7.6.2, include the following:

- **Prep D1** (K_2 EDTA whole blood collection optimized for DNA analysis): A 4 mL blood biospecimen will be collected on or prior to Cycle 1 Day 1; Cycle 1 Day 15 (Arm A only); Day 1 of Cycles 2, 3, and 5; and at the End of Treatment/Withdrawal Visit. All collections must be pre-dose.

- **Prep B2 (serum collection optimized for biomarker/proteomic/metabonomic analysis)**: A 10 mL blood biospecimen will be collected on or prior to Cycle 1 Day 1; Cycle 1 Day 15 (Arm A only); Day 1 of Cycles 2, 3, and 5; and at the End of Treatment/Withdrawal Visit. All collections must be pre-dose.

- **Prep B1 (EDTA plasma collection optimized for biomarker/proteomic/ metabonomic analysis)**: A 10-mL blood biospecimen will be collected on or prior to Cycle 1 Day 1; Cycle 1 Day 15 (Arm A only); Day 1 of Cycles 2, 3, and 5; and at the End of Treatment/Withdrawal Visit. All collections must be pre-dose.

The banked biospecimens will be collected from all patients **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

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

7.6.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, patients will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions.
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Patients need not provide additional biospecimens for the uses described in this section; the biospecimens specified in the Markers of Drug Response section will be used. Patients may still participate in the clinical study if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.7. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans. Bone imaging, eg, bone scans or other methods considered standard of care locally, such as ^{18}FDG PET or MRI, are required at baseline (28 day screening period). (**Note**: ^{18}FDG-PET may not be a permissible alternate for bone imaging at some centers or countries (eg, investigative sites in Canada).) Bone lesion(s) identified at baseline by bone scan will be further assessed by CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by CT or MRI as per the tumor assessment schedule as an alternative to bone scans. Bone imaging will only be repeated during study as clinically indicated (eg, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), at the time of complete response (CR) confirmation, and at every other tumor assessment visit (ie, every 16 weeks for the first year after randomization and every 24 weeks thereafter) if considered local standard of care.

Brain imaging (eg, MRI) is required at baseline for patients who have a history of brain metastases or for whom brain metastases are suspected during screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases at baseline; otherwise brain will only be evaluated when clinically indicated.

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.

Both pre-chemotherapy and post-chemotherapy scans must have been performed and be readily available during screening. The post-chemotherapy confirmatory scan for eligibility must be performed within 28 days prior to the date of randomization to assess response status following first-line chemotherapy. This scan will also be used as the baseline scan for tumor assessments in this study.

All radiographic images from the time of the most recent tumor assessment prior to first-line chemotherapy until documented disease progression will be submitted to an independent third-party core imaging laboratory for BICR as described in Study Manual.

For all patients, anti-tumor activity will be assessed through radiological tumor assessments (including chest, abdomen, and pelvic CT or MRI scans) conducted at baseline (ie, the post-chemotherapy confirmatory scan for randomization), every 8 weeks up to 1 year after randomization, and every 12 weeks thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumor assessments should also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

Assessment of response will be made using RECIST version 1.1 (Appendix 2). Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless an increase in size has been observed following completion of radiation therapy.

CR and PR must be confirmed with repeat imaging performed at least 4 weeks after initial documentation of response. In the absence of clinical deterioration, patients with PD should remain on the current study treatment until PD is confirmed by BICR. For Arm A patients, please see Section 5.4.1 regarding continued avelumab study treatment after initial evidence of disease progression.

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

As per Protocol Amendment 6, following the final OS update, tumor assessments will be performed by the study investigator at a frequency as per local standard of care and when progression is suspected. Radiologic images will no longer be submitted for independent central review or entered into the CRF.

7.8. Expedited Blinded Independent Central Review for Disease Progression

Prior to implementation of Protocol Amendment 6 and the final OS update, to mitigate the potential for bias in determining disease progression, expedited BICR will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from baseline onwards will be submitted to the BICR for expedited review. See the Study Manual for process details. Every effort should be made to keep the patient on study treatment until the BICR has completed their imaging review.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment (Arm A) or 90 days after the EOT visit (Arm B). SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least 1 dose of study treatment (Arm A) or from Cycle 1 Day 1 (Arm B) through and including 90 calendar days after the last administration of study treatment (Arm A) or 90 days after the EOT visit (Arm B).

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

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

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

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

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

8.3.1. Avelumab Adverse Events of Special Interest

Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section 5.4.3.4. AESIs are reported according to the general AE reporting rules specified in Section 8.1 and Section 8.2.

8.4. Medication Errors

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

Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

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

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

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

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

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE (version 4.03) Grade 5 (see Section 8.8 Severity Assessment).

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

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section 8.14.1, Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who

present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

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

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

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

- **Concurrent with**

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

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

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

8.7. Hospitalization

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

however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study treatment 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 study treatment caused the event, then the event will be handled as "related to study treatment" for reporting purposes, as defined by the sponsor (see Section 8.14, Reporting Requirements). If the investigator's causality assessment is "unknown but not related to study treatment", 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

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

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).

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion.

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

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

the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (also see Section 6.5 Patient Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient or legally acceptable representative. In addition, each study patient or legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

For Investigative Sites in Japan Only:

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary objective of this study is to demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging OS in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary UC patient populations: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients.

The study will randomize a total of approximately 668 patients, with at least 334 patients with confirmed PD-L1-positive tumors, using 1:1 randomization, stratified by best response to chemotherapy (CR/PR vs. SD) and site of metastasis (visceral vs. non-visceral) at time of initiating first-line chemotherapy. The "non-visceral" stratum includes patients with locally-advanced disease as well as patients with only non-visceral disease. The type 1 error rate will be split between the co-primary populations to preserve the overall type 1 error rate for the study at 0.025 one-sided. It is estimated that at least 50% of the randomized patients will have adequate tissue for analysis and be determined to have PD-L1-positive tumors.

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

- For all patients and patients with PD-L1-positive tumors receiving BSC alone after first-line chemotherapy, the median OS is 12 months.[33]
- For all patients receiving avelumab plus BSC after first-line chemotherapy, the median OS is assumed to be 17.1 months.
- For patients with PD-L1-positive tumors receiving avelumab plus BSC after first-line chemotherapy, the median OS is assumed to be 18.5 months.

This corresponds to a hazard ratio (HR) of 0.7 for all patients and 0.65 for patients with PD-L1-positive tumors under the exponential model assumption.

For all patients, if the true HR is 0.7 under the alternative hypothesis, a total of 425 OS events will be required to have 93% power to detect a HR of 0.7 using a one-sided log rank test at a significance level of 0.015 and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming)[71] α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.

For patients with PD-L1 positive tumors, if the true HR is 0.65 under the alternative hypothesis, then a total of 219 OS events will be required to have 80% power to detect a HR of 0.65 using a one-sided log rank test at a significance level of 0.01 and a 2-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary (see Section 9.6 Interim Analysis for details).

The sample size further assumes a 5% drop-out rate for OS on either treatment arm, a non-uniform patient accrual accomplished over a 28-month period, and follow-up for about

11 months after the last patient is randomized. The data cutoff for the primary OS analysis will occur after the target number of events has been reached in both co-primary populations and the last patient randomized in the study has been followed for at least 12 months after randomization.

The study will be considered positive if the stratified log rank test for OS is significant at the respective adjusted levels at the interim or at the final analyses, for either of the two co-primary populations.

9.2. Analysis Populations

9.2.1. Full Analysis Set

The Full Analysis Set will include patients who are randomized. Patients will be classified according to the treatment and stratum assigned at randomization. The Full Analysis Set will be the primary analysis set for evaluating all efficacy endpoints and patient characteristics within each of the co-primary populations: 1) patients determined to have PD-L1-positive tumors (including infiltrating immune cells) by a verified GMP PD-L1 IHC test and 2) all randomized patients.

Patients to be included in the co-primary population defined by PD-L1 positive tumors will be determined by retrospective analysis of the mandatory recent FFPE tumor biospecimen (see Sections 4.1 and 6.1.1) using an analytically-validated and GMP-verified PD-L1 IHC assay with a pre-specified scoring algorithm defining PD-L1 positive status. The PD-L1 IHC assay and scoring algorithm will be fully defined prior to initiation of sample analysis.

9.2.2. Per-Protocol Analysis Set

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

9.2.3. Safety Analysis Set

The Safety Analysis Set will include all patients who receive at least 1 dose of avelumab or who only receive BSC. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received. The Safety Analysis Set will be the primary population for evaluating treatment administration/compliance and safety.

9.2.4. PK Analysis Set

The PK Concentration Analysis Set will include all treated patients who have at least 1 concentration above the below limit of quantitation (BLQ) of avelumab.

The PK Parameter Analysis Set will include all treated patients who have at least 1 of the PK parameters of interest.

9.2.5. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all treated Arm A patients who have at least 1 ADA sample collected.

9.2.6. Biomarker Analysis Set

The Biomarker Analysis Set will include all treated Arm A patients who have at least 1 baseline biomarker assessment performed.

9.3. Efficacy Analysis

All efficacy analyses will be performed on the Full Analysis Set within each of the co-primary populations unless otherwise specified.

All analyses will be performed by using SAS® Version 9.1.3 or higher.

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

The primary analysis will be repeated on the Per-Protocol Analysis Set as a sensitivity analysis. Further sensitivity analyses will be described in the SAP.

9.3.1. Analysis of Primary Endpoint

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

The primary analyses of OS will be performed based on the Full Analysis Set. A stratified log-rank test (one-sided) stratified by stratification factors described in Section 3 will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at its respective levels (one-sided 0.015 for all patients and one-sided 0.01 for patients with PD-L1-positive tumors). OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI.

OS will also be evaluated based on the PPS as a sensitivity analysis using the stratified log-rank test with the overall significance level preserved at its respective levels (one-sided 0.015 for all patients and one-sided 0.01 for patients with PD-L1-positive tumors).

9.3.2. Analysis of Secondary Endpoints

All analyses will be performed using the Full Analysis Set separately for each co-primary population. The analysis of PFS using the Full Analysis Set described in Section 9.2.1 based on BICR assessment will be repeated based on the investigator's assessment.

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

Progression-Free Survival

PFS is defined as the time from randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any post-baseline tumor assessments will be censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

Within each co-primary population PFS time will be summarized by treatment arm using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th, and 75th percentiles of the event-free time will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CI.

Objective Response (OR)

Objective response is defined as a CR or PR according to RECIST v1.1 (Appendix 2) recorded from randomization 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. A patient will be considered to have achieved an OR if the patient has a sustained CR or PR according to RECIST v1.1 definitions. Otherwise, the patient will be considered as a non-responder in the ORR analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the ORR analysis.

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

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

Time to Tumor Response (TTR)

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

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

Duration of Response (DR)

Duration of response (DR) is defined, for patients with an objective response per RECIST v1.1, as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS.

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

Disease Control (DC)

Disease control (DC) is defined as complete response (CR), partial response (PR), non-CR/non-PD, or stable disease (SD) according to the RECIST v.1.1 (Appendix 2) recorded from randomization 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. Criterion for SD must have been met at least 6 weeks after the date of randomization.

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

Patient Reported Outcomes (PRO) Endpoints

The FBlSI-DRS-P subscale will be used to determine the Time to Deterioration (TTD). TTD is defined as the time from first dose (baseline) to the first time the patient's score shows a 3 point or higher decrease in the FBlSI-DRS-P subscale. Patients will be censored at the last time when they completed a sub-scale assessment if they have not deteriorated. Kaplan-Meier plots will be used to display deterioration over time and a log-rank test will be used to compare the TTD between the two treatment arms. The median time and 2-sided 95% CI for the median will be provided based on the Brookmeyer Crowley method.[72]

Yost & Eton (2005)[73] established that a 3-point or a greater minimally important difference (MID) from baseline on the FACT scales would correlate with change in disease symptoms and status. Thus, in the analysis of TTD, a MID of 3 points or greater is proposed within the FBlSI-DRS-P sub-scale of the NCCN-FACT FBlSI-18. Additionally, symptom sub-scale improvement will be defined as an increase of at least 3 points in the mean FBlSI-DRS-P sub-scale score of the NCCN-FACT FBlSI-18. Within group and between group comparisons to baseline in order to assess symptom improvement among treatment arms will also be performed. To test the robustness of the MID of 3 points, sensitivity analyses using 2 and 4 points will be explored.

Patient reported disease/treatment related symptoms of bladder cancer, function/well-being, and general health status will also be assessed. Summary statistics [mean (and SE), median, range and 95% CI] of absolute scores will be reported for all of the subscales of the NCCN-FACT FBlSI-18 questionnaire and the EQ-5D-5L VAS scale. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm. Additional exploratory analyses may be performed, such as repeated measures mixed effects modeling and analyses of patients who experienced a complete response.

Pharmacokinetic Analysis of Avelumab

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

Immunogenicity Assessment

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

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

Analysis of Biomarker Endpoints

Analyses to evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in addition to PD-L1 expression defining the co-primary population may also be performed in which biomarker status (ie, positive or negative) will be determined in all randomized patients by a predictive biomarker test with an established scoring algorithm defining positive and negative that is developed by the sponsor. Analysis of primary and secondary efficacy endpoints in subgroups defined by biomarker status will be performed and reported as described above. Comparisons will be made between biomarker subgroups (positive and negative) within treatment arms and between treatment arms within biomarker subgroups.

Exposure/Response Analysis

In addition, the relationship between exposure and efficacy and safety endpoints may be explored, as necessary, based on emerging efficacy and safety data. Refer to the SAP for details. The results of these modeling analyses may be reported separately from the clinical study report.

9.4. Analysis of Other Endpoints

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

9.4.1. Statistical Analysis of Biomarker Endpoints

It is possible that, during the course of this study, emerging data and/or methods will suggest additional patient selection strategies beyond the verified GMP PD-L1 test used to define the co-primary populations. Retrospective analysis of biomarkers such as PD-L1 (using a different method from the GMP test) and CD8 are planned as a secondary objective to enable refinements in patient selection strategy, whether via technical modifications or revised thresholds. These methods may be single- or multi-analyte based on IHC or immunofluorescence. Further exploratory analyses may also be performed to assess the predictive and/or pharmacodynamic utility of additional methods, such as profiling of gene expression signatures indicative of immune activation. The Biomarker Analysis Set will be used for the analysis of biomarker endpoints.

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

Data from biomarker assays will be analyzed using graphical methods and descriptive statistics such as linear regression, t-test, and analysis of variance (ANOVA). The statistical approach may examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

Regarding exploratory biomarkers, the data analysis will be conducted with the goal of identifying predictive and/or pharmacodynamic (ie, baseline and change from baseline values) biomarkers associated with clinical outcome, encompassing both safety and efficacy. Candidate biomarkers will be validated in subsequent trials.

9.4.2. Exploratory Endpoints

Details regarding exploratory endpoints (definitions and analyses) will be provided in the SAP.

9.5. Safety Analysis

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

Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible (http://ctep.info.nih.gov/reporting/ctc.html). The frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term will be reported. Adverse events will be graded by worst NCI CTCAE v4.03 Grade. Adverse events will be summarized by cycle and by relatedness to study treatment.

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for AEs of clinical interest may be further assessed as described in the SAP.

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

Laboratory Abnormalities

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

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

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

9.6. Interim Analysis

The interim analysis will be performed based on the Full Analysis Set.

The purposes of the interim analysis are to: (i) allow early stopping of the study for futility, (ii) to allow early stopping of the study for efficacy, (iii) to assess safety of avelumab, and (iv) to potentially adjust the sample size. The interim analysis for both co-primary populations will be performed at the same time.

The interim analysis of OS will be performed after at least 315 of all randomized patients have died (74% of the total OS events needed), and all of the following conditions have been met:

i. All initially planned patients have been randomized; and

ii. At least 146 patients with PD-L1-positive tumors have died (approximately 66.7% of the total OS events expected in the PD-L1-positive tumor population).

The efficacy and futility boundaries for the co-primary populations with the planned number of events at interim look are listed below in Table 8. The boundary values will be updated using the pre-specified α and β spending functions with the observed number of events at the time of the interim analysis. The study may be stopped if:

- The futility boundary is crossed for both populations (all and PD-L1+); or
- The efficacy boundary is crossed for both populations (all and PD-L1+); or
- The futility boundary is crossed for one of the populations and the efficacy boundary is crossed for the other population.

Alternatively, as appropriate, the sample size of the study may be adjusted using the method outlined by Cui et al [1999].[74] If the results of the interim analysis indicate serious safety concerns, the sponsor, in conjunction with the External Data Monitoring Committee (E-DMC), will communicate with the Health Authorities regarding stopping the clinical trial.

Table 8. Stopping Boundaries for Overall Survival

Population	Number of Events	Efficacy		Futility	
		Z scale	p-value (one-sided)	Z scale	p-value (one-sided)
All patients	315	z < -2.595	p <0.005	z > -0.789	p >0.215
PD-L1-positive	146	z < -2.947	p <0.002	z > -0.397	p >0.346

9.7. External Data Monitoring Committee

This study will use an E-DMC.

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

The E-DMC will convene to monitor safety in the study approximately every 6 months.

Following the pre-planned interim analysis at which the primary objective was met, the E-DMC had completed its study-specific activities and was therefore closed.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

For Investigative Sites in Japan Only:

After avelumab is approved for treatment of advanced urothelial carcinoma by the MHLW in Japan, Japanese investigators will conduct this study according to Japanese Good Post-Marketing Surveillance Practices (GPSP) in addition to Good Clinical Practice (GCP).

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

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

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

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

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any

study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in all other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. ECOG Performance Status

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

Appendix 2. Response Evaluation Criteria in Solid Tumors 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 short axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

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

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

Normal sites

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

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

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

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

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

Non-target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

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

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

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

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

- Indeterminate. Progression has not been documented, and

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

    or

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

    or

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

    or

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

Non-target disease

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

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

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence

of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

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

New Lesions

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

Supplemental Investigations

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

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

Objective/Subjective Progression

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

Table 9. Objective Response Status at each Evaluation

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

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

Table 10. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum on study). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. CR and PR must be confirmed by 2 measurements at least 4 weeks apart. In the case of SD, follow up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Appendix 3. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

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

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

Appendix 4. Cockcroft-Gault Formula

[(140-Age) * Mass (in kg)] / [72 * Serum creatinine (in mg/dL)].

If the patient is female, multiply the above by 0.85.

Appendix 5. Abbreviations and Definitions of Term

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

^{18}FDG PET/CT	^{18}Fluorodeoxyglucose positron emission tomography/computed tomography
ACTH	Adrenocorticotropic hormone
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacille Calmette-Guérin
BICR	Blinded Independent Central Review
BSC	Best Supportive Care
BUN	Blood urea nitrogen
CG	Cockcroft-Gault
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CSA	Clinical Study Agreement
CT	Computed tomography scan
CTA	Clinical Trial Application
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	Cardiac troponin subunit I
cTnT	Cardiac troponin subunit T
DAI	Dosage and Administration Instructions
DC	Disease Control
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DR	Duration of response
DU	Dispensable unit
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy

EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 dimension 5 level questionnaire
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FBlSI	FACT-Bladder Cancer Symptom Index
FBlSI–DRS-P	NCCN-FACT FBlSI-18 Disease Related Symptoms-Physical subscale
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practices
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GPSP	Good Post-Marketing Surveillance Practices
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International normalized ratio
ir	Immune-related
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation in Solid Tumors
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intra-uterine hormone-releasing system
IV	Intravenous
IVR	Interactive voice response
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MID	Minimally important difference
MHLW	Ministry of Health, Labor and Welfare
MRI	Magnetic resonance imaging
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
Nab	Neutralizing antibody
NCI	National Cancer Institute

NSAID	Nonsteroidal anti-inflammatory drug
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PES	Polyether sulfone
PFS	Progression-free survival
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PRO	Patient Reported Outcome
PS	Performance status
PT	Prothrombin time
Q2W	Every two weeks
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SD	Stable disease
SRSD	Single reference safety document
SOA	Schedule of Activities
SST	Serum separator tube
SUSAR	Serious unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TGF	Transforming growth factor
TLS	Tumor lysis syndrome
TNM	Tumor Node Metastasis
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
TTR	Time to tumor response
UC	Urothelial cancer
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WBC	White blood cell

Appendix 6. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures is expected to cease upon the return of business as usual (including the lifting of any quarantines and travel bans/advisories).

1.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit, if applicable as per the SOA in effect at the time of the visit:

- Review and record any AEs and SAEs since the last contact. Refer to protocol Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing (Arm A only). Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 1.2.1 of this appendix regarding pregnancy tests.
- ECOG PS
- Patient Reported Outcomes
- Survival Assessment

Study participants must be reminded to promptly notify site staff about any change in their health status.

1.2. Alternative Facilities for Safety Assessments

1.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Required laboratory safety assessments as per protocol Section 7.1.3.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

1.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Avelumab cannot be administered outside of the investigational site. If the patient cannot visit the site, the infusion will be omitted.

The following is recommended for the administration of avelumab for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, avelumab should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions for any concomitant medication administered for treatment of SARS-CoV2 infection.

1.4. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

1.5. Efficacy Assessments

Survival: Collection as per SOA should continue for study patients in Follow-up.

Tumor assessments: Tumor assessments by CT/MRI are to be performed as per protocol requirements at the investigational site/facilities to the extent possible.

- If a different imaging facility is used, please notify the site monitor and update the form FDA 1572 as appropriate.

- The investigational site should advise the imaging facility to obtain the images consistent with the study 'Imaging Acquisition Guidelines' and to transmit the resulting images to the investigational site.

Patient-Reported Outcome: In the event that study patients cannot come to the site for in-clinic visits, these assessments should be performed remotely (eg, via telephone). The study site staff performing the remote visit are to read the instructions, questions, and response choices verbatim and mark the response choice selected by the study patient.

- Conduct this telephone call in a quiet, private area and ask the patient to also go to a place where they are alone (ie, no one else around and/or able to provide input or influence their responses).

- Please read the full text including all instructions, questions, and response options. Please ensure you are speaking clearly and at a comfortable pace. Also, let the study patient know that you can re-read the instructions, question, or response options at any time.

- Do not interpret any part of the questionnaire for the study patient. If the study patient does not understand, please repeat the question and response choices verbatim and ask them to select the response that they feel best represents his/her experience.

- Confirm the study patient's response selection before you record the answer (eg, you would like me to select "moderate pain", is that right?).

- Indicate on the paper questionnaire that it was performed via remote visit (eg, via telephone). Include the name of the study site staff performing the remote visit and confirm that the study patient was the one to answer the questions.

- Add an Investigator Comment on both PRO questionnaire CRFs to indicate "Assisted due to COVID-19."

1.6. Patient Discontinuation

- Required in-clinic visits, including Avelumab administrations, may be missed without causing discontinuation from the maintenance treatment phase of the study. However, all study patient withdrawal criteria listed in Protocol Section 6.5 remain applicable.

- For study patient discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

- It's important to continue to enter the CRF data as quickly as possible, so we have access to the data for safety monitoring. If the sponsor determines that the impact of COVID-19 on protocol visits and procedures and associated timeframes needs to be reported on a case report form (CRF), this will be requested.

17. SUPPLEMENT 1: CROSSOVER FROM BSC ALONE (ARM B) TO AVELUMAB PLUS BEST SUPPORTIVE CARE

This supplement provides details for patients in the BSC alone arm who crossover to receive avelumab plus BSC. All other information in the protocol not addressed in this supplement still apply. After 60 days following the final OS update or approval of Amendment 6, whichever is later, no additional Arm B patients will be allowed to crossover to avelumab plus BSC.

ELIGIBILITY CRITERIA

Inclusion Criteria

Patients randomized to Arm B must meet all of the following inclusion criteria to be eligible to crossover from BSC alone to avelumab plus BSC:

1. Patients randomized to Arm B (BSC alone) ongoing in the maintentance phase (ie, patients must not have completed the EOT visit).

2. Patients without progressive disease while on study as per RECIST v1.1 guidelines as assessed by the investigator.

3. Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guideline/practice) has been informed of the aspects of crossover.

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

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

6. Adequate bone marrow function, including:

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

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

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

7. Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation (Appendix 4) or by 24-hour urine collection for creatinine clearance or according to the local institutional standard method.

8. Adequate liver function, including:

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

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5 × ULN.

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

2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be eligible to crossover from BSC alone to avelumab plus BSC:

1. Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to avelumab treatment (Cycle CR1 Day 1). Prior palliative radiotherapy is permitted, provided it has been completed at least 48 hours prior to avelumab treatment (Cycle CR1 Day 1).

2. Patients with known symptomatic central nervous system (CNS) metastases requiring steroids. Patients with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to randomization, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.

3. 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.

4. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

5. Active infection requiring systemic therapy.

6. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3), any history of anaphylaxis, or uncontrolled asthma (ie, 3 or more features of asthma symptom control per the Global Initiative for Asthma 2015).[66]

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

8. Current or prior use of immunosuppressive medication within 7 days prior to avelumab treatment (Cycle CR1 Day 1), EXCEPT the following:

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

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

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

9. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy.

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

11. Breastfeeding female patients and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in the protocol Section 4.3.1 for the duration of the study and for at least 30 days after the last dose of investigational product.

12. Other severe acute or chronic medical conditions including but not limited to HIV, HBV, or HCV infection, colitis, inflammatory bowel disease, pneumonitis, and pulmonary fibrosis; 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 study treatment 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.

GENERAL TREATMENT/STUDY PLAN

Patients who crossover from BSC alone to avelumab plus BSC will receive avelumab at 10 mg/kg on Day 1 and Day 15 of each 4-week treatment cycle after all procedures/assessments have been completed as described in the SOA table.

With the exception of the detailed SOA provided below, all study treatments, concomitant medication restrictions, AE reporting, etc, described for patients randomized to Arm A in Section 5 through Section 7.1 and Section 8 of the study protocol will be followed for patients who crossover from Arm B to avelumab plus BSC.

SCHEDULE OF ACTIVITIES FOR PATIENTS WHO CROSSOVER FROM ARM B TO AVELUMAB PLUS BSC

The SOA provides an overview of the protocol visits and procedures for patients randomized to Arm B who are eligible to crossover to receive avelumab plus BSC. 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. If deemed clinically necessary, the investigator may schedule visits in addition to those listed in the SOA table (unplanned visits) at any time to conduct evaluations or assessments required to protect the well-being of the patient. Following implementation of Protocol Amendment 6 and the final OS update, all patients will follow the "PROTOCOL AMENDMENT 6: SCHEDULE OF ACTIVITIES FOR STUDY TREATMENT, END OF TREATMENT AND FOLLOW-UP PERIODS."

CROSSOVER FROM ARM B TO AVELUMAB PLUS BSC

Visit Identifiers[1]	**Screening**	**Avelumab plus BSC (1 cycle = 4 weeks)**	
	Within 28 Days Prior to Avelumab	**Cycle CR1 Day 1**[1] **CR Cycle ≥2 Day 1 (±3 days)**	**Day 15 (±3 days) All CR Cycles**
Clinical Assessments			
Informed Consent[2]	X		
Baseline Signs/Symptoms[3]		X (Cycle CR1 only)	
Physical Examination[4]	X	X	
ECOG Performance Status	X	X	
Vital Signs and Weight[5]	X	X	X
Contraception Check[6]	X	X	X
Laboratory Studies			
Coagulation[7]	X	X	X
Hematology[7]	X	X	X
Blood Chemistry (full and core)[7,8]	X	X	X
Thyroid Function and ACTH Tests[9]	X	X (at Cycles CR3, 5, 7, etc.)	
Serum/Urine Pregnancy Test[10]	X	X	X
Troponin[11]	X	X (Cycles CR1-4 and as clinically indicated)	X (Cycles CR1-3 and as clinically indicated)
Urinalysis[12]	X	If clinically indicated	
12-Lead ECG[13]	X	If clinically indicated	

CROSSOVER FROM ARM B TO AVELUMAB PLUS BSC

Visit Identifiers[1]	Screening	Avelumab plus BSC (1 cycle = 4 weeks)	
	Within 28 Days Prior to Avelumab	Cycle CR1 Day 1[1] CR Cycle ≥2 Day 1 (±3 days)	Day 15 (±3 days) All CR Cycles
Disease Assessments			
Tumor Assessments (including scans)[14]		X	
Other Clinical Assessments			
Adverse Events[15]	X	X	X
Concomitant Medications/Treatments[16]	X	X	X
Study Treatment			
Avelumab[17]		X	X
Best Supportive Care (BSC)[18]		X (Throughout study treatment)	

ACTH = adrenocorticotropic hormone; BSC = best supportive care; CR = crossover; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group

Footnotes for SCHEDULE OF ACTIVITIES FOR SCREENING AND STUDY TREATMENT PERIOD

1. **Visit Identifiers:** All assessments should be performed prior to dosing with avelumab unless otherwise indicated. Cycle CR1 Day 1 pre-dose assessments completed within 7 days prior to dosing do not need to be repeated unless clinically indicated. Acceptable time windows for performing each assessment are described in the column headers. **Note**: laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.
2. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedure.
3. **Baseline Signs/Symptoms:** To be recorded on Cycle CR1 Day 1. Patients will be asked about any signs and symptoms experienced within the 14 days prior to Cycle CR1 Day 1.
4. **Physical Examination:** Includes an examination of major body systems.
5. **Vital Signs and Weight:** Vital signs to include blood pressure and pulse rate, which should be taken prior to study drug dosing (if applicable) and with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
   Weight should be measured at each visit as indicated. Weight should be measured within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]).
6. **Contraception Check:** Female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use the selected contraception methods consistently and correctly and document such conversations in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the male patient's partner. See Section 4.3.1.
7. **Coagulation, Hematology, and Blood Chemistry (full panel)**: Required tests are listed in Table 6. Full chemistry panel is required at Screening, Cycle CR1 Day 1, Cycle CR1 Day 15, Cycle CR2 Day 1, Cycle CR3 Day 1, and Day 1 of every 2 cycles (8 weeks) thereafter. May also be performed when clinically indicated. If full and core chemistry panels are scheduled at the same visit, only the full chemistry will be performed.
8. **Blood Chemistry (core panel)**: Core chemistry panel (required tests are listed in Table 6) is required at each clinic visit at which a full chemistry panel is not required.

9. **Thyroid Function and ACTH Tests:** Free T4, TSH, and ACTH tests will be performed at screening, Cycle CR3 Day 1, and Day 1 of every 2 cycles (8 weeks) thereafter. Additional tests should be performed when clinically indicated. See Table 6.
10. **Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting avelumab: once at the start of screening and once at the Cycle CR1 Day 1 visit immediately before study treatment administration. Additional pregnancy tests (serum or urine) will also be routinely repeated prior to each avelumab dose during the active treatment period, at the End of Treatment/Withdrawal visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. Results of the pregnancy test should be available prior to each dosing. See Section 7.1.1.
11. Cardiac Troponin (cTn): Measurement of cTnT is preferred; however, cTnI may be substituted where cTnT is not available at the local laboratory. The same subunit (cTnT or cTnI) measured during screening should be measured consistently throughout the study for any given patient. During screening, clinically significant positive results should be further assessed as per local standard of care to rule out concurrent cardiac conditions which could make the patient ineligible for the study per the exclusion criteria. During the study, clinically significant new elevations suggestive of myocarditis should be assessed as per Table 5. Additional tests should also be performed when clinically indicated. See Table 6.
12. Urinalysis: Required only at Screening and End of Treatment. To be performed as clinically indicated at other time points. Required tests are listed in Table 6.
13. 12-Lead Electrocardiogram (ECG): A single ECG measurement is required at screening. Additional ECGs may be performed as clinically indicated. Clinically significant new findings seen on follow-up ECGs should be recorded as adverse events.
14. **Tumor Assessments:** Tumor assessments will be performed according to the local standard of care and when progression is suspected, however the tumor assessment data will no longer be entered into the CRF nor submitted for central imaging review.
15. **Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor. AEs (serious and non-serious) should continue to be recorded on the Case Report Form (CRF) through and including 90 calendar days after the last administration of avelumab. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.
16. Concomitant Medications/Treatments: Concomitant medications and treatments should continue to be recorded through and up to 90 days after the last dose of avelumab. If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new cancer therapy is started; see Section 5.9 for additional details. All concomitant medications will be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant medications should be reviewed at each study visit, and any prohibited treatments (as described in Section 5.9) should be discussed with the patient and appropriately managed.
17. **Avelumab Treatment:** Avelumab (10 mg/kg) will be given as a 1-hour intravenous infusion every 2 weeks. Patients should be weighed within 3 days prior to each dose of avelumab (for determination of the avelumab dose [mg]). All safety assessments must be performed and results reviewed by the treating physician prior to avelumab administration. Patients with disease progression who are continuing to derive clinical benefit from study treatment will be eligible to continue with avelumab provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.4.1).
18. Best supportive care (BSC): See Section 5.8. All BSC components must comply with the permitted medications described in this protocol (see Section 5.9).

CROSSOVER FROM ARM B TO AVELUMAB PLUS BSC: END OF TREATMENT/WITHDRAWAL AND FOLLOW-UP					
Visit Identifiers[1]	**End of Treatment/ Withdrawal (±3 days)[2]**	**Follow-up[3]**			
		Short-Term			**Long-Term every 3 months (±14 days)**
		30 days (±3 days) After Last Dose	**60 days (±3 days) After Last Dose**	**90 days (±3 days) After Last Dose**	
Clinical Assessments					
Physical Examination[4]	X	X	X	X	
ECOG Performance Status	X	X	X	X	
Vital Signs and Weight[5]	X	X	X	X	
Contraception Check[6]	X	X			
Laboratory Studies					
Hematology[7]	X	X	X	X	
Blood Chemistry (full panel)[8]	X	X	X	X	
Coagulation[7]	X	X	X	X	
Thyroid Function Tests and ACTH[9]	X	X	X	X	
Serum/Urine Pregnancy Test[10]	X	X			
Urinalysis[11]	X				
12-lead ECG[12]	If clinically indicated				
Disease Assessments					
Tumor Assessments (including scans)[13]	X				
Other Clinical Assessments					
Adverse Events[14]	X	X	X	X	
Concomitant Medications/Treatments[15]	X	X	X	X	
New Systemic Anticancer Treatment	X	X	X	X	X
Survival Assessment[16]		X	X	X	X

ACTH = adrenocorticotropic hormone; BSC = best supportive care; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group

Footnotes for SCHEDULE OF ACTIVITIES FOR END OF TREATMENT/WITHDRAWAL AND FOLLOW-UP PERIODS
1. **Visit Identifiers:** Acceptable time windows for performing each assessment are described in the column headers. Per the visit time window, laboratory tests may be performed up to 3 days prior to the scheduled clinic visit so that results will be available for review.
2. **End of Treatment/Withdrawal:** Obtain these assessments if not completed in the prior week, except for tumor assessments, which need not be repeated if performed within the prior 6 weeks.

3.	**Short- and Long-Term Follow-up:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of avelumab. During the post-treatment safety follow-up (beyond 30 days through 90 calendar days after last avelumab administration), AEs (serious or non-serious) that the investigator believes have at least a reasonable possibility of being related to study drug are to be recorded on the case report form (CRF). Beyond the 90 days until the end of the study (long-term follow-up), all patients will be followed every 3 months after the last study clinic visit (±14 days) for survival, tumor assessment, and new systemic anticancer treatment; additional timepoints to collect survival information may be requested by the Sponsor in preparation for interim and final analyses.
4.	**Physical Examination:** Includes an examination of major body systems.
5.	**Vital Signs and Weight:** Vital signs to include blood pressure and pulse rate. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
6.	**Contraception Check:** Female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception until at least 30 days after the last dose of avelumab. The investigator or his or her designee will discuss with the patient the need to use the selected contraception methods consistently and correctly and document such conversations in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if the selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the male patient's partner. See Section 4.3.1.
7.	**Hematology, Blood Chemistry, and Coagulation**: Required tests are listed in Table 6. May also be performed when clinically indicated.
8.	**Blood Chemistry:** Full chemistry panel (see Table 6) is required at End of Treatment/Withdrawal and during short-term follow-up visits (Days 30 ±3, 60 ±3, 90 ±3 after last dose).
9.	**Thyroid Function Tests:** Free T4, TSH, and ACTH will be performed at the End of Treatment/Withdrawal and at Follow-up visits at 30±3, 60±3, and 90 ±3 days after last dose of avelumab. Additional tests should be performed when clinically indicated. See Table 6.
10.	**Serum/Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the End of Treatment/Withdrawal visit and at the 30-Day Follow-up visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRB)/Ethics Committees (ECs) or if required by local regulations. See Section 7.1.1.
11.	**Urinalysis**: Required only at the End of Treatment/Withdrawal. To be performed as clinically indicated at other time points. Required tests are listed in Table 6.
12.	**12-Lead Electrocardiogram (ECG):** When clinically-indicated. Clinically significant new findings seen on follow-up ECGs should be recorded as adverse events. See Section 7.1.5 for further details.
13.	**Tumor Assessments:** Tumor assessments will be performed according to the local standard of care and when progression is suspected, however the tumor assessment data will no longer be entered into the CRF nor submitted for central imaging review.
14.	**Adverse Events:** Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For serious adverse events (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study treatment, through and including 90 calendar days after the last administration of the study treatment. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study treatment are to be reported to the sponsor. AEs (serious and non-serious) should continue to be recorded on the Case Report Form (CRF) through and including 90 calendar days after the last administration of avelumab. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of study treatment, irrespective of any intervening treatment.

15.	**Concomitant Medications/Treatments**: Concomitant medications and treatments should continue to be recorded through and up to 90 days after the last dose of avelumab. If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new cancer therapy is started; see Section 5.9 for additional details. All concomitant medications will be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant medications should be reviewed at each study visit, and any prohibited treatments (as described in Section 5.9) should be discussed with the patient and appropriately managed.
16.	**Survival Assessment:** All patients will be followed for survival and subsequent anticancer therapies every 3 months (±14 days) after the last study clinic visit until death, end of the study, or patient withdrawal of consent, whichever comes first. These visits may be conducted in-clinic or by remote contact (eg, telephone). Additional timepoints to collect survival information may be requested by the Sponsor in preparation for interim and final analyses.