A MULTICENTER, OPEN-LABEL, PHASE 1B/2 STUDY TO EVALUATE SAFETY AND EFFICACY OF AVELUMAB (MSB0010718C) IN COMBINATION WITH CHEMOTHERAPY WITH OR WITHOUT OTHER ANTI-CANCER IMMUNOTHERAPIES AS FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED MALIGNANCIES

JAVELIN CHEMOTHERAPY MEDLEY

Investigational Product Number:	MSB0010718C
Investigational Product Name:	Avelumab (MSB0010718C)
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Phase:	1b/2

Document History

Document	Version Date	Summary of Changes and Rationale
Original Protocol	26 May 2017	Not applicable (N/A)
Protocol Amendment 1	07 August 2017	The following changes to the original protocol were requested by the FDA: • In response to the request that the protocol focus only on Group A (avelumab plus chemotherapy), all text and all table content, as well as Figure 2, pertaining to Group B (avelumab plus chemotherapy plus PF-06840003), any study treatment to be used in Group B, and any background information pertaining to any part of Group B were removed throughout the protocol. • In response to the request that carboplatin/pemetrexed dosing in Cohort A1 be limited to 4-6 cycles with the option to continue pemetrexed dosing as maintenance therapy, text reflecting this request was added to the Phase 2 Cohort Expansion section of the Protocol Summary, Study Treatment Section of the Protocol Summary, Table 1 and Footnote 16 of Table 1, Section 3 Study Design, and Section 5.2 Treatment Duration. • In response to the request that premedication instructions be included in the protocol, instructions from the pemetrexed United States Prescribing Information were added to Section 5.4.2.1 Dosage and Administration for chemotherapy agents. Text was also added indicating that local guidelines are to be followed if different if from the USPI. In addition, the following changes were implemented: • In Section 1.2.1.3, Clinical Experience in Patients with Locally Advanced or Metastatic UC, text was revised to include information about recent FDA approval. Efficacy data were updated to reflect that presented in avelumab (Bavencio®) prescribing

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		information. • Section 1.2.1.4, Clinical Experience in Patients with Recurrent or Metastatic SCCHN, was removed given this tumor type will not be evaluated in the amended study. • Section 4.1 Inclusion Criteria, the words "OR and have" were removed from Criterion 10a to clarify that postmenopausal status may be confirmed with a follicle-stimulating hormone level test. • Section 4.2 Exclusion Criteria, the words "and/or during study participation" were removed from Criterion 18 because this text referred to the patient's status after enrollment rather than serving as eligibility guidance. • Section 5.2, Treatment Duration, text concerning treatment discontinuation/continuation was updated to improve clarity. • In Table 14 in Section 7.1.4, Laboratory Safety Assessments, "bile acids" was added to Footer "a" for potential Hy's law evaluation to align table with guidance in Section 8.4.2 Potential Cases of Drug-Induced Liver Injury.
Protocol Amendment 2	19 January 2018	The following changes to the 07 August 2017 Protocol Amendment 1 will be introduced in response to the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) observations for UK sites and will apply only to UK sites: • In response to the request that the protocol is limited to the evaluation of the Group A study drug combinations or to a limited number of groups and number of cohorts within a group, the sentence "For the UK: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included" is added in several Sections.

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		• In response to the request that condom plus spermicide not be noted as a highly effective method of contraception, the sentence "For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate" in Section 4.3 has been modified to read "For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception (eg, the UK), this option is not appropriate."
Protocol Amendment 3	15 March 2018	In response to the Czech Republic State Institute for Drug Control's (SUKL) observations, the phrase "and the Czech Republic" is added to the same changes included in Protocol Amendment 2 for sites in the UK, as indicated in the text below: • The sentence "For the UK: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included" which was added in several Sections in Protocol Amendment 2 is modified to read "For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included" to indicate that only a limited number of study drug combinations and tumor types will be evaluated at sites in the Czech Republic. • In Section 4.3, the sentence "For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception (eg, the UK), this option is not appropriate" is modified to read "For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception (eg, the UK and the Czech Republic), this option is not appropriate" in response to the request that, in the Czech Republic, condom plus spermicide not be noted as a highly effective method

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		of contraception.
Protocol Amendment 4	02 October 2018	The following changes to the 15 March 2018 Protocol Amendment 3 are introduced: • Introduction of a higher fixed dose of avelumab (based on US FDA feedback). The Phase 1b portion of the study is amended to include the evaluation of 1200 mg fixed dose avelumab administered Q3W in combination with chemotherapy in both the NSCLC (Cohort A3) and UC (Cohort A4) cohorts, after the initial 800 mg Q3W dose has cleared the dose-limiting toxicity (DLT) assessment period and is deemed safe, according to the current study design. Feedback from the FDA's review of the original protocol included a recommendation to evaluate additional avelumab doses, indicating that target occupancy alone is insufficient to support dose selections. All text and all tables' content, as well as Figure 1 mentioning Cohorts A1 and A2, are updated to introduce Cohorts A3 and A4 and the rules allowing enrollment in those cohorts, throughout the protocol. • The total number of patients enrolled in the two cohorts (NSCLC and UC) in Phase 1b and Phase 2 remains unchanged at up to approximately 80 patients. However, a higher number of patients will be enrolled in Phase 1b overall to permit evaluation of the safety of the combination of the fixed dose avelumab administered at 800 mg and at 1200 mg Q3W with chemotherapy. Therefore, in order to keep the total number of enrolled patients at 80 and to retain the cohort size of 40 patients with UC (in Phase 1b and Phase 2), the number of patients in the NSCLC cohort (Phase 2) is reduced. All text and all tables' content mentioning sample size are updated to reflect this modification. • In order to add flexibility about expansion of the cohorts from Phase 1b Lead-in to Phase 2, the following sentences "enrollment will be initiated" or "expansion will be initiated" have been updated to

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		read "enrollment may be initiated" or "expansion may be initiated" respectively, at various points throughout the protocol. • Section 1.2.3 Study Rationale as well as the Protocol Summary, are updated to present the introduction of the 1200 mg fixed dose avelumab administered Q3W in combination with chemotherapy. • Section 1.3 Summary of Benefit/Risk Assessment, text is revised to include safety information from clinical trials for the 20 mg/kg every 2 weeks dose of avelumab. In addition, the following changes are implemented: • Section 1.4 Biomarker Rationale, text is revised to include information about the use of biopsy data from patients receiving the 1200 mg avelumab fixed dose. • Section 4.1 Inclusion Criteria, Criterion 1 is updated to accept archived tumor sample of 18 months instead of 1 year. A clarification is added about eligibility of patients with only one measurable (target) lesion. • Section 4.1 Inclusion Criteria, Criterion 10b is updated to include "and/or bilateral salpingectomy" to align text with current Pfizer standard protocol template for Phase 1-4 studies. • Section 4.1 Exclusion Criteria, Criterion 22 is updated to be in line with latest version of the Pfizer protocol template language for contraception. • Section 4.3 Lifestyle Guidelines, text is revised to be in line with latest version of the Pfizer protocol template language for contraception. • Section 5.4.3 Timing of Investigational Product Administrations, text is updated to clarify administration interval beween chemotherapy and avelumab infusions.

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		• Sections 5.4.4.1, 5.4.4.7.1, 5.4.4.7.2, 5.4.4.8.1, and 5.4.4.8.2, have been updated to specify that dose modifications due to adverse drug reactions should be made in accordance with the guidance in the protocol, product labeling, and institutional guidelines. • Section 5.4.4.2 Dose Delays: All Investigational Products text is revised to add clarifications to the recommended dose delays guidelines. • Section 5.4.4.7.1 Hematological Toxicities, text is revised to add clarifications to the recommended dose modifications guidelines. • Sections 5.4.4.8.1 and 5.4.4.8.2, have been updated to specify that dose adjustments following dose delays due to toxicities, should start at the subsequent dose rather than "start of a subsequent cycle". • Table 11 Pemetrexed, Carboplatin, Avelumab (Cohorts A1 and A3) Non- Hematologic Toxicity Management, text is revised to add clarifications to the recommended dose modifications guidelines. • Section 5.4.4.8.1 Hematological Toxicities, text is revised to add clarifications to the recommended dose modifications guidelines. • Table 12 Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Hematologic Toxicity Management, text is revised to add clarifications to the recommended dose modifications guidelines. • Table 13 Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Non-Hematologic Toxicity Management, text is revised to add clarifications to the recommended dose modifications guidelines. • Section 5.4.5 Treatment after Initial Evidence of Radiological Disease Progression, text is updated to clarify that avelumab should be permanently discontinued in case of further disease progression. A clarification is also added about the timelines of

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		subsequent radiologic imaging. • Section 5.7 Concomitant Medications, text is updated to clarify that the collection of concomitant medications should end when a patient begins a new anti-cancer therapy. • Section 6.1.1 Tumor Biospecimens, text is updated to accept archived tumor sample of ≤18 months instead of 1 year. A clarification is added about eligibility of patients with only one measurable (target) lesion. • Section 7.1.2 Contraceptive Check, text is updated to be in line with latest version of the Pfizer protocol template language for contraception. • Section 7.1.6 (12-Lead) Electrocardiogram, text is updated for procedure clarification. • Section 7.6 Tumor Response Assessments, text is updated to clarify the methods to be used for bone imaging and the time schedule for bone imaging assessments. • Section 9.5.1 Analysis of Pharmacokinetics of Study Drugs, text is updated to remove time to maximum plasma concentration (T_{max}) estimation for avelumab and chemotherapy agents as all drugs are administered intravenously. • Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines, update is added to clarify that all required scans must be done within 28 days prior to first dose of study treatment instead of prior to enrollment. • At various points throughout protocol, all text pertaining to immune-related response criteria (irRECIST) including objectives, endpoints, tumor assessments, and Appendix 4, is removed in an effort to reduce burden on sites for determining and reporting tumor response per irRECIST criteria.

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		• Additional procedural clarifications, not previously mentioned, are added according to two previously issued Protocol Administrative Changes Letters as follow: • Section 6.2 Treatment Period, text is updated for inclusion of a statement about study treatment continuation at the end of study. • Section 7.6 Tumor Response Assessments, text is updated for clarification of windows around scheduled tumor assessments. • Section 8.1.4 Time Period for Collecting AE/SAE Information, text is updated for clarification of wording for guidance for AE/SAE information collection. • Schedule of Activities Table 1 and Table 3 Footnote 9, text is updated for clarification of laboratory results that must be available and reviewed prior to study drug administration. CCI [redacted] • Schedule of Activities Table 1 and Table 3 Footnote 39 (deleted), text is updated for removal of collection of blood sample for analysis of kynurenine and tryptophan. • Schedule of Activities Table 1 and Table 3 Footnote 39, text is updated for clarification of window for Day 1 visits post Cycle 1.

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

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PROTOCOL SUMMARY

Indication

Avelumab is a human anti-programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 isotype that is currently being investigated in combination with other anti-cancer immunotherapies to enhance antitumor activity over that expected by avelumab alone in patients with locally advanced or metastatic solid tumors. Avelumab is expected to increase the effectiveness of antitumor T cells by preventing inhibition of T cell activation. Combination of avelumab with agents that enhance the immune response by different mechanisms would be expected to lead to an increase in antitumor activity over that seen with avelumab alone. This study will initially investigate avelumab in combination with standard-of-care chemotherapy and, in portions of the study to be added in the future, with or without other anti-cancer immunotherapies as first-line therapy for patients with advanced or metastatic solid tumors. For the United Kingdom (UK) and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

Background and Rationale

There are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[4,5] Chemotherapy has been shown to have immunostimulatory properties via its ability to promote the release of neoantigens and to enhance antigen uptake and presentation via the process of immunogenic cell death, hence leading to an increase in immune priming against the tumor. In addition, a number of chemotherapies have been shown to alter the immunogenicity of tumor cells both at the cell intrinsic level, through modulation of cell surface proteins like major histocompatibility complex (MHC), and also at the cell extrinsic level, through depletion of suppressive elements within the microenvironment such as regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs).[6-9]

Several immune checkpoint inhibitors have been combined with chemotherapy agents. Of particular relevance to Study B9991023 are results from studies of programmed death-1 (PD-1)/PD-L1 inhibitors plus platinum doublet chemotherapy as first-line therapy in patients with advanced or metastatic non-small cell lung cancer (NSCLC). In a Phase 2 cohort of the KEYNOTE-021 study,[27] the combination of carboplatin and pemetrexed with or without pembrolizumab was evaluated in patients with advanced non-squamous NSCLC. A significant increase in objective response rate (objective response rate [ORR], 55%; 95% confidence interval [CI] 42-68%) was noted for the triplet therapy relative to ORR for chemotherapy alone (29%; 95% CI 18-41%). In addition, progression-free survival (PFS) for patients treated with the triplet was significantly greater than that for chemotherapy-treated patients (hazard ratio [HR] 0.53 [95% CI 0.31-0.91] p=0.010). Based on data from the KEYNOTE-021 study, on 10 May 2017, the Food and Drug Administration (FDA) approved pembrolizumab in combination with carboplatin and pemetrexed for the first-line treatment of patients with metastatic non-squamous NSCLC, irrespective of PD-L1 expression.[52]

Overall these clinical and preclinical data are supportive of the potential for increased antitumor activity through the combination of chemotherapy and avelumab.

This study will investigate avelumab in combination with standard-of-care chemotherapy with or without other anti-cancer immunotherapies as first-line therapy for patients with advanced malignancies. Initially, avelumab will be evaluated in combination with standard-of-care chemotherapy in patients with advanced non-squamous NSCLC and cisplatin-eligible urothelial cancer (UC). These two tumor types were selected for study because they are responsive to chemotherapy, which currently is first-line standard-of-care for these indications. In addition, avelumab has shown preliminary evidence of clinical activity in both non-squamous NSCLC and UC.

Given the growing preclinical and clinical findings that combinations of anti-cancer immunotherapies potentially improve patient outcomes compared to results seen with single agents, in portions of the study to be added in the future, avelumab will be evaluated in combination with both standard-of-care chemotherapy and other anti-cancer immunotherapies in patients with advanced malignancies.

Initially avelumab will be dosed at 800 mg every 3 weeks (Q3W). Once the safety of this dose of avelumab in combination with each of the two chemotherapy regimens has been determined, additional cohorts of patients will be enrolled at the higher avelumab dose of 1200 mg Q3W. The proposed avelumab fixed dosing regimens of 800 mg Q3W and 1200 mg Q3W are expected to reach >90% target occupancy (TO) throughout the 21-day dosing interval in the majority of patients, including when used in combination with chemotherapy or other anti-cancer immunotherapies. The 1200 mg Q3W dosing regimen is being explored additionally in this Phase 1b/2 trial as it is projected to maintain the avelumab average exposures close to those observed with the approved dose of 10 mg/kg every 2 weeks (Q2W) while extending the dosing interval for use in combination with Q3W chemotherapy regimens.

Addition of new therapy combinations will be based on emerging preclinical and clinical data supportive of the tolerability and potential clinical benefit of each agent to be combined (eg, chemotherapy, anti-cancer immunotherapy agents) with avelumab and will be accomplished by protocol amendment. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

Study Objectives and Endpoints

Primary Objectives

- Phase 1b lead-in: To assess dose limiting toxicity (DLT) rate of avelumab in combination with chemotherapy, as first-line treatment in patients with locally advanced or metastatic solid tumors.

- To assess, per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1, the ORR of avelumab in combination with chemotherapy, as first-line treatment in patients with locally advanced or metastatic solid tumors.

Secondary Objectives

- To assess the overall safety and tolerability of avelumab in combination with chemotherapy;
- To characterize the pharmacokinetics (PK) of avelumab and chemotherapy when given in combination;
- To evaluate the immunogenicity of avelumab, when given in combination with chemotherapy;
- To assess the antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy;
- To assess the correlation of antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy, with mutational load in baseline tumor tissue;
- To assess the correlation of PD-L1expression in baseline tissue and changes in this marker on-treatment, with antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy.

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Endpoints

Primary Endpoints

- Phase 1b lead-in: First 2 cycles DLT.
- Confirmed objective response (OR), as assessed by the Investigator using RECIST v1.1.

Secondary Endpoints

- Adverse events (AEs) as characterized by type, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03), timing, seriousness, and relationship to study treatments;
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03), and timing;
- PK parameters of avelumab;
- PK parameters of chemotherapies, as data permit;
- Anti-drug antibody (ADA) levels;
- Time-to-event endpoints including PFS, duration of response (DR), and time to tumor response (TTR), as assessed by the Investigator using RECIST v1.1; and overall survival (OS);
- Mutational load within baseline tumor tissue;
- PD-L1 expression in baseline and on-treatment tumor tissue.

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Study Design

This is a Phase 1b/2, open-label, multi-center, safety, clinical activity, PK, and PD study of avelumab in combination with chemotherapy with or without other anti-cancer immunotherapies, as first-line treatment of adult patients with locally advanced or metastatic solid tumors. Incorporation of the chemotherapy and other anti-cancer immunotherapies into this study is based on preclinical and clinical data supportive of the tolerability and potential clinical benefit of each agent to be combined (eg, chemotherapy, anti-cancer immunotherapy agents) with avelumab. Initially, avelumab will be evaluated in Group A in combination

with standard-of-care chemotherapy in patients with advanced malignancies as described below. Additional combinations of avelumab plus standard-of-care chemotherapy with or without other anti-cancer immunotherapy agent(s), other than other anti-PD-1/PD-L1 mAb, may be incorporated via protocol amendment into future portions of the study based on emerging preclinical and clinical data. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

- Group A: avelumab plus chemotherapy:
    - Cohort A1: avelumab 800 mg Q3W plus pemetrexed/carboplatin in patients with non-squamous NSCLC;
    - Cohort A2: avelumab 800 mg Q3W plus gemcitabine/cisplatin in patients with cisplatin-eligible UC;
    - Cohort A3: avelumab 1200 mg Q3W plus pemetrexed/carboplatin in patients with non-squamous NSCLC;
    - Cohort A4: avelumab 1200 mg Q3W plus gemcitabine/cisplatin in patients with cisplatin-eligible UC.

Each combination cohort will be studied in 2 phases: 1) a Phase 1b lead-in to evaluate preliminary safety of the combination, and 2) a Phase 2 cohort expansion to evaluate preliminary efficacy and further evaluate safety. Phase 2 cohort expansion may be initiated only for the highest dose level of avelumab deemed safe for the combination.

Phase 1b Lead-in

The safety of avelumab will be assessed independently in combination with each of the two different chemotherapy regimens.

The 1200 mg Q3W dosing regimen is being explored additionally in this Phase 1b/2 trial since it is projected to maintain the avelumab average exposures close to those observed with the approved dose of 10 mg/kg Q2W while extending the dosing interval for use in combination with Q3W chemotherapy regimens.

Up to 12 patients will be enrolled into each cohort and evaluated for DLT during the first 2 cycles of treatment as follows:

Cohorts A1 and A2

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:
    - If ≤1 of 6 patients experience DLT in Cohort A1 (or A2), enrollment may be initiated in Phase 1b Cohort A3 (or A4);

- If ≥3 of up to 6 patients experience DLT in Cohort A1 (or A2), enrollment in Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination;

- If 2 of 6 patients experience DLT in Cohort A1 (or A2), the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b Cohort A1 (or A2);

    - If ≤3 of 12 patients experience DLT in Cohort A1 (or A2), enrollment may be initiated in Phase 1b Cohort A3 (or A4);

    - If ≥4 of up to 12 patients experience DLT in Cohort A1 (or A2), enrollment in the Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination.

Cohorts A3 and A4

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:

    - If ≤1 of 6 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy; there will not be any enrollment in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy.

    - If ≥3 of up to 6 patients experience DLT in Cohort A3 (or A4), enrollment in Cohort A3 (or A4) will be discontinued; enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy.

    - If 2 of 6 patients experience DLT in Cohort A3 (or A4), the Cohort A3 (or A4) will be expanded to enroll up to 6 additional DLT-evaluable patients:

        - If ≤3 of 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy; there will not be any enrollment in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;

        - If ≥4 of up to 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy.

Phase 2 Cohort Expansion

If investigational products administration in the Phase 1b Lead-in portion of a given cohort is deemed safe based on the criteria described in "Phase 1b Lead-in" Section, then enrollment into that cohort may continue into the Phase 2 Cohort Expansion. The dose of avelumab to be administered in the Phase 2 Cohort Expansion (800 mg Q3W for Cohorts A1 and A2 or 1200 mg Q3W for Cohorts A3 and A4) will be determined based on the number of observed DLTs as described in "Study Design". The highest dose level of avelumab deemed safe for the combination will be advanced.

For the cohort of patients with cisplatin-eligible UC selected to expand into Phase 2, up to approximately 40 patients including those enrolled in the Phase 1b Lead-in and those enrolled in the Phase 2 Cohort Expansion, will be treated with avelumab plus chemotherapy in the initial portion of the study and, in future portions of the study, with avelumab plus chemotherapy with or without other anti-cancer immunotherapies. For the cohort of patients with non-squamous NSCLC selected to expand into Phase 2, approximately 20 patients including those enrolled in the Phase 1b Lead-in and those enrolled in the Phase 2 Cohort Expansion will be treated with avelumab plus chemotherapy in the initial portion of the study and, in future portions of the study, with avelumab plus chemotherapy with or without other immunotherapies. Up to approximately 80 patients with cisplatin-eligible UC and non-squamous NSCLC will be enrolled in Group A (Phase 1b Lead-in and Phase 2 Cohort Expansion).

In future portions of the study, up to approximately 40 patients in each cohort (including those enrolled in the Phase 1b Lead-in and those enrolled in Phase 2) will be enrolled and treated with avelumab plus chemotherapy in the initial portion of the study and, in future portions of the study, with avelumab plus chemotherapy with or without other anti-cancer immunotherapies. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

For both Phase 1b lead-in and Phase 2 cohort expansion, all patients will initially receive either avelumab in combination with chemotherapy (Group A) or avelumab in combination with chemotherapy and other anti-cancer immunotherapies in future portions of the study. Patients will continue to receive study treatment until disease progression is confirmed by the Investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. In Cohorts A1 and A3, treatment with carboplatin and pemetrexed will continue for a maximum of 4-6 cycles; in addition, maintenance therapy with pemetrexed may be administered at the discretion of the Investigator. In Cohorts A2 and A4, treatment with chemotherapy will continue until optimal response is achieved.

If discontinuation of chemotherapy is required for any reasons other than progressive disease (PD) or protocol-specified limits, treatment with avelumab (Group A) (or avelumab and/or the other anti-cancer immunotherapies in future portions of the study) should be continued.

Patients who stop avelumab (or the other anti-cancer immunotherapies in future portions of the study) for unacceptable toxicity may continue treatment with the investigational product(s) (eg, chemotherapy) that is/are not considered to be responsible for the toxicity observed.

Tumor Assessments

Antitumor activity will be assessed by radiological tumor assessments at 6-week intervals, using RECIST v1.1. In case partial response (PR) or complete response (CR) is observed according to RECIST v1.1, tumor assessments should be repeated at least 4 weeks after initial documentation. After 1 year from the first dose of study treatment, tumor assessments will be conducted at 12-week intervals until PD per RECIST v1.1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

Safety Assessments

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

Pharmacokinetic/Immunogenicity Assessments

PK and immunogenicity blood sampling will be collected for each combination as described in the Schedule of Activities and Section 7.2.

Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and chemotherapy with or without other immunotherapies. C
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[redacted] For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

Study Treatments

Avelumab 800 mg (Cohorts A1 and A2) or 1200 mg (Cohorts A3 and A4) fixed dose will be administered as a 1-hour (hr) intravenous (IV) infusion on Day 1 of each 21-day cycle.

Each chemotherapy doublet will be administered IV as shown below per local guidelines.

Investigational Product	Dose(s) and Schedule (21-day cycle)[a,b]	Cohorts	Tumor Type
Avelumab[c]	800 mg or 1200 mg, Day 1 IV over 60 minutes	All	All
Pemetrexed/Carboplatin		A1, A3	Non-squamous NSCLC
Pemetrexed	500 mg/m^2, Day 1 IV over 10 minutes		
Carboplatin	AUC 5, Day 1 IV over 60 minutes		
Gemcitabine/Cisplatin		A2, A4	UC
Gemcitabine	1000 mg/m^2, Day 1 and Day 8 IV over 30 minutes		
Cisplatin	70 mg/m^2, Day 1 IV over 60 minutes		

AUC=area under the curve; IV=intravenous; NSCLC=non-small cell lung cancer; UC=urothelial cancer

[a] Order of administration is as appears in the table. For example, for the pemetrexed/carboplatin doublet, pemetrexed is administered prior to carboplatin.

[b] Durations of chemotherapy infusions shown are recommended. Sites are advised to follow their local guidelines.

[c] Avelumab dosed at 800 mg Q3W in Cohorts A1 and A2 and at 1200 mg Q3W in Cohorts A3 and A4.

Treatment with chemotherapy in Cohorts A1 and A3 will continue for a maximum of 4-6 cycles, with pemetrexed continuing as maintenance at the Investigator's discretion, and in Cohorts A2 and A4 until optimal response is achieved. For all cohorts (A1, A2, A3 and A4), chemotherapy and avelumab may be discontinued in the event of disease progression confirmed by the Investigator, patient refusal, unacceptable toxicity, patient lost to follow-up, or until the study is terminated by the Sponsor, whichever occurs first.

Statistical Methods

Phase 1b Lead-in: DLTs will be assessed in the DLT-evaluable patients in each cohort then enrollment into the cohort will be expanded into Phase 2 cohort expansion.

The table below shows the probability of meeting DLT requirements to escalate to the dose level of avelumab 1200 mg Q3W in combination with chemotherapy. For example, for a DLT that occurs in 10% of patients, the probability of confirming safety and escalating to avelumab 1200 mg Q3W is approximately 0.97.

Probability of Escalating Dose Level of Avelumab to 1200 mg Q3W after Phase 1b Lead-in of Each Cohort (A1 and A2)

True underlying DLT rate[a]	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose level of avelumab	0.97	0.82	0.56	0.31	0.14	0.05	0.01	0.002	<0.0001

[a] True underlying DLT rate for the combination of avelumab 800 mg Q3W with chemotherapy.

Phase 1b Lead-in and Phase 2 Cohort Expansion combined: The primary endpoint for the Phase 1b lead-in and the Phase 2 cohort expansion combined is the confirmed OR as assessed by the Investigator using RECIST v1.1.

OR is defined as a CR or PR per RECIST v1.1, from the first dose of study treatment until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of patients with a confirmed CR or PR per Investigator's assessment according to RECIST v.1.1.

Based on safety data for patients with cisplatin-eligible UC, the Phase 1b lead-in from either Cohort A2 (800 mg avelumab plus chemotherapy) or Cohort A4 (1200 mg avelumab plus chemotherapy) may be selected to continue enrollment into the Phase 2 cohort expansion. Up to approximately 40 patients with cisplatin-eligible UC, including Phase 1b lead-in and Phase 2 cohort expansion patients, may receive the selected avelumab dose plus chemotherapy.

Based on safety data for patients with non-squamous NSCLC, the Phase 1b lead-in from either Cohort A1 (800 mg avelumab plus chemotherapy) or Cohort A3 (1200 mg avelumab plus chemotherapy) may be selected to continue enrollment into the Phase 2 cohort expansion. Up to approximately 20 patients with non-squamous NSCLC, including Phase 1b lead-in and Phase 2 cohort expansion patients, may receive the selected avelumab dose plus chemotherapy.

With 40 patients in the UC cohort and 20 patients in the NSCLC cohort, with Phase 1b and Phase 2 combined, ORR can be estimated with a maximum standard error of 0.079 and 0.112, respectively. Within each cohort, ORR will be estimated and the two-sided exact 90% confidence interval will be calculated.

SCHEDULE OF ACTIVITIES

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

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

Table 1. SCHEDULE OF ACTIVITIES: Non-squamous NSCLC – Avelumab + Pemetrexed/Carboplatin, Cohort A1 and A3

		On-Treatment: One cycle = 21 days					Post-Treatment		
	Screening	Immunotherapy + Chemotherapy				Immunotherapy			
Protocol Activities[1]	Within 28 Days Prior to Enrollment	Pemetrexed/Carboplatin/Avelumab				Avelumab	End of Treatment +7 days[22]	Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]	Long-Term Follow-up (Every 12 weeks ±14 days[24]
		Cycles 1 – 3			Cycles ≥4				
		Day 1 ±2 days[39]	Day 8 ±2 days	Day 15 ±2 days	Day 1 ±2 days	Day 1 of each cycle ±2 days			
Clinical Assessments									
Informed Consent[2]	X								
Medical/Oncological History[3]	X								
Baseline Signs/Symptoms[4]	X								
Physical Examination[5]	X	X		X	X	X	X	X	
ECOG Performance Status[6]	X	X		X	X	X	X	X (Day 30 only)	
Vital Signs and Weight[7]	X	X		X	X	X	X	X	
Contraceptive Check[8]	X	X			X	X	X	X	
Laboratory Studies									
Hematology[9]	X	X	X	X	X	X	X	X	
Blood Chemistry[9]	X	X	X	X	X	X	X	X	
Coagulation[9]	X	X			X	X	X	X	
Thyroid Function/ACTH[10]		Day 1 of Cycle 1, Cycle 4 and every 3 cycles thereafter					X	X	
Urinalysis[11]	X	If clinically indicated					X		
Pregnancy Test[12]	X	X			X	X	X	X	
HBV and HCV Tests[13]	X								
12-Lead ECG[14]	X	X			If clinically indicated				
Enrollment and Study Treatment									
Enrollment[15]		X							
Pemetrexed Administration[16]		X			X	X[16]			
Carboplatin Administration[16]		X			X				
Avelumab Administration[17]		X			X	X			
Disease Assessments									
Tumor Assessments/Scans[18]	X	Cycle 3 Day 1 (±2 days), then every 6 weeks (±2 days). After 1 year from first dose of study drug, every 12 weeks (±14 days) until progressive disease regardless of initiation of new anti-cancer treatment							

Table 1 SCHEDULE OF ACTIVITIES: Non-squamous NSCLC - Avelumab + Pemetrexed/Carboplatin, Cohorts A1 and A3 (continued)

		On-Treatment: One cycle = 21 days					Post-Treatment		
	Screening	Immunotherapy + Chemotherapy				Immunotherapy			
Protocol Activities[1]	Within 28 Days Prior to Enrollment	Pemetrexed/Carboplatin/Avelumab				Avelumab	End of Treatment + 7 days[22]	Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]	Long-Term Follow-up (Every 12 weeks ±14 days)[24]
		Cycles 1 – 3			Cycles ≥4				
		Day 1 ±2 days[39]	Day 8 ±2 days	Day 15 ±2 days	Day 1 ±2 days	Day 1 of each cycle ±2 days			
Other Clinical Assessments									
Serious and Non-serious Adverse Event Monitoring[19]	X	Monitored and recorded throughout treatment					X	X	
Concomitant Treatments[20]	X	Monitored and recorded throughout treatment					X	X	
Short- and Long-Term Follow-up After Last Dose of Study Treatment									
Subsequent Anti-Cancer Treatments[21]								X	X
Short-term Follow-up Assessments[23]								X	
Long-term/Survival Assessment[24]								X	X
Samples for Pharmacodynamic, Pharmacokinetic, CCI Analyses									
De Novo Tumor Biopsy or Archival FFPE Tumor Tissue Block[25]	X								
On-Treatment Tumor Biopsy[26]			X Cycle 2 only (-7 days to +2 days)						
End of Treatment Tumor Biopsy[27]							X		
Avelumab PK[28]		X		X	X (select cycles)	X (select cycles)			
Anti-Avelumab Antibodies (ADA)[29]		X			X (select cycles)	X (select cycles)	X		
Pemetrexed PK[30]		X (Cycle 2 subset patients)	X (Cycle 2 subset patients)						

Table 1 SCHEDULE OF ACTIVITIES: Non-squamous NSCLC – Avelumab + Pemetrexed/Carboplatin, Cohorts A1 and A3 (continued)

		On-Treatment: One cycle = 21 days					Post-Treatment		
	Screening	Immunotherapy + Chemotherapy				Immunotherapy			
Protocol Activities[1]	Within 28 Days Prior to Enrollment	Pemetrexed/Carboplatin/Avelumab				Avelumab	End of Treatment +7 days[22]	Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]	Long-Term Follow-up (Every 12 weeks ±14 days[24]
		Cycles 1 – 3			Cycles ≥4				
		Day 1 ±2 days[39]	Day 8 ±2 days	Day 15 ±2 days	Day 1 ±2 days	Day 1 of each cycle ±2 days			
Carboplatin PK[31]		X (Cycle 2 subset patients)	X (Cycle 2 subset patients)						

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ACTH=adrenocorticotropic hormone; BID=twice daily; ECG=electrocardiogram; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed, paraffin-embedded; HBV=Hepatitis B virus; HCV=Hepatitis C virus; PK=pharmacokinetics; CCI [redacted]

Footnotes for Table 1 SCHEDULE OF ACTIVITIES

1. **Protocol Activities:** All assessments should be performed prior to study treatment dosing unless otherwise indicated. Acceptable time windows for performing each assessment are provided in the column headers.

2. **Informed Consent:** Must be obtained prior to the patient undergoing any study-specific procedure.
3. **Medical/Oncological History:** Both medical and oncological histories are to be collected within 28 days prior to first dose of study treatment. Medical history should include history of other disease (active or resolved) as well as concomitant illnesses. Oncological history should include information on prior regimens (including dosing and duration of therapy, best overall response, and disease recurrence/progression date), surgery, and radiation therapy.
4. **Baseline Signs/Symptoms:** To be recorded on the Medical History CRF form. Patients will be asked about any signs and symptoms experienced within the 14 days prior to signing the informed consent document. After signing the informed consent document, any new or worsening conditions since baseline should be reported on the AE CRF.
5. **Physical Examination:** Includes an examination of major body systems (height included at screening only).
6. **ECOG Performance Status:** ECOG performance scale may be found in Appendix 2. Determination of ECOG Performance Status will continue through the 30-day Follow-Up visit unless the patient has started on a new anti-cancer therapy.
7. **Vital Signs and Weight:** See Section 7.1.5.
8. **Contraception Check:** See Section 4.3 and Section 7.1.2.
9. **Coagulation, Hematology, and Blood Chemistry (full panel)**: Cycle 1 Day 1 tests do not need to be repeated if they have been conducted in the prior 3 days and data are available for review. Full hematology and full clinical chemistry tests must be performed. Full hematology panel as well as AST, ALT, and creatinine results must be reviewed by medically-qualified study personnel prior to each administration of study drug. Results from all other laboratory assessments are not required to be reviewed prior to study drug dosing, unless there are signs or symptoms to suggest an underlying lab abnormality. However, all lab results should be reviewed as soon as they are available. Laboratory tests may be performed up to 3 days prior to each scheduled visit so that results will be available for review. Required tests are listed in Section 7.1.4. Full chemistry panel is required at Screening, Day 1, Day 8, and Day 15 of Cycles 1 through 3; Day 1 of every subsequent cycle; End of Treatment; and at the 30-day follow-up visit. Core chemistry panel (required tests are listed in Section 7.1.4) is required at Follow-Up Day 60 and Day 90. Coagulation and hematology are required as noted in this table. If the patient permanently discontinues chemotherapy before Cycle 4, but continues on avelumab and/or other anti-cancer immunotherapies in future portions of the study, then chemistry and hematology samples should be obtained at Day 1 of subsequent cycles. Any test may also be performed when clinically indicated. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.
10. **Thyroid Function/ACTH Tests**. Additional tests should be performed when clinically indicated. See Section 7.1.4.
11. **Urinalysis**: Required only at Screening and End of Treatment. To be performed if clinically indicated at other time points. Required tests are listed in Section 7.1.4.
12. **Serum/Urine Pregnancy Test:** Results of the pregnancy test must be available prior to each study treatment dosing. See Section 7.1.1.
13. **HBV and HCV Tests:** HBV surface antigen and anti-HCV antibody will be performed at Screening. HCV RNA will be performed if anti-HCV antibody test is positive (Section 7.1.4, Table 14).
14. **12-Lead Electrocardiogram (ECG):** All patients require triplicate ECG measurements at screening and on treatment. On treatment triplicate ECGs will be performed on Day 1 of Cycles 1 to 3, before (pre-dose) and at the end of avelumab infusion for all patients. See Table 2 for ECG monitoring of subset of patients undergoing serial PK collection in Cohorts A1 and A3. See Section 7.1.6.
15. **Enrollment:** Study treatment must be initiated preferably on the day of enrollment, but no later than 3 days after enrollment. Patients meeting all entry criteria will be registered and enrolled using the Interactive Response Technology system. See Section 5.1.

16. **Pemetrexed/Carboplatin Administration:** Pemetrexed 500 mg/m^2 and carboplatin area under curve (AUC) 5 will be administered IV both on Day 1 of every 21-day cycle for a maximum of 4-6 cycles. After this time, pemetrexed therapy may continue as maintenance at the Investigator's discretion. Premedication will be administered as specified in Section 5.4.2.1. On visits when both chemotherapy and avelumab are infused (Day 1 of each 21-day cycle), chemotherapy will be infused before avelumab. See Section 5.4.3. See Section 5.2 for guidance on treatment duration.
17. **Avelumab Administration:** Avelumab 800 mg will be administered Q3W (Day 1 of each 21-day cycle). 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 intravenous infusion on Day 1 of each 21-day cycle. On visits when both chemotherapy and avelumab are infused (Day 1 of each 21-day cycle), avelumab will be infused *after* chemotherapy but within 30 minutes (+20-minute time window if needed) of the end of the chemotherapy infusion, see Section 5.4.3. See Section 5.4.1.3 for guidance on required premedication for avelumab infusion. See Section 5.2 for guidance on treatment duration.
18. **Tumor Assessments:** For patients with NSCLC, tumor assessments by CT or MRI scans will include chest and abdomen at all time points. For patients with NSCLC, pelvic assessments will be conducted only if clinically indicated at baseline or at any subsequent point. Baseline scans must be performed within 28 days prior to first dose of study drug. See Section 7.6 for complete information.
19. **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) v 4.03. See Section 8.1.4 for guidance on the time period for collecting and reporting AE and SAEs. If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the active collection period.
20. **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, see Section 5.7.
21. **Subsequent Anti-Cancer Treatments:** These treatments will be documented and recorded for patients who discontinue all study treatments and continue in the Short –term and Long-Term Survival periods of the study.
22. **End of Treatment (discontinuation of all study drugs for any reason):** Obtain these assessments if not completed in the prior 7 days.
23. **Short-Term Follow-Up after Last Dose of Study Treatment:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first. See Section 6.3 for guidance on tumor assessment during Short-term Follow-up.
24. **Long-Term Follow-up (Survival):** Following completion of the end of treatment visit, all patients will be followed for survival and subsequent anti-cancer treatments every 12 weeks (±14 days) until death, end of the study, or patient withdrawal of consent, whichever comes first. See Section 6.3 for guidance on tumor assessment during Long-term Follow-up.
25. ***De Novo* Tumor Biopsy and Archival FFPE Tumor Tissue Block**: See Section 6.1.1.
26. **On-Treatment Tumor Biopsy:** See Section 6.1.1.
27. **At Progression Tumor Biopsy:** An optional *de novo* tumor sample is encouraged to be collected at End of Treatment if a patient discontinues due to disease progression. See Section 6.1.1.
28. **Blood for Avelumab Pharmacokinetics:** Blood samples (3.5 mL whole blood at each specified time point) will be collected from all patients in the study at pre-dose and 1 hour post-start of avelumab infusion (ie, at the end of infusion) on Day 1 of Cycles 1, 2, 3, 6, 10, and 14; an additional sample will be collected during the Day 15 visit of Cycle 1, 2, and 3. See Section 7.2.1.

29. **Blood for Anti-Avelumab Antibodies (Anti-Drug Antibodies: ADA):** Blood samples (3.5 mL whole blood at each specified time point) for avelumab immunogenicity testing will be collected from all patients pre-dose on Day 1 of Cycles 1, 2, 3, 6, 10, and 14, and at End of Treatment. See Section 7.3.
30. **Blood for Pemetrexed Pharmacokinetics (only in subset of patients undergoing serial PK):** See Table 2 and Section 7.2.2.2.
31. **Blood for Carboplatin Pharmacokinetics (only in subset of patients undergoing serial PK):** See Table 2 and Section 7.2.2.1.

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[redacted]

39. The visit window for Day 1 visits post Cycle 1 during study treatment is ±2 days.

Table 2. PK and ECG ASSESSMENTS (Only for Subset of Patients Undergoing Serial PK): Non-squamous NSCLC – Avelumab + Pemetrexed/Carboplatin, Cohorts A1 and A3

	Cycle 1				Cycle 2						
	Day 1		Day 15		Day 1					Day 8[6]	Day 15[6]
	Time after start of pemetrexed infusion (hr)				Time after start of pemetrexed infusion (hr)						
	Pre-dose	3.0			Pre-dose	0.17 (10 min)	1.5	3.0	5.5		
All Cohorts:											
Blood for Pemetrexed PK[1]					X	X	X		X	X	
Blood for Carboplatin PK[2]					X		X	X	X	X	
Blood for Avelumab PK[3]	X	X	X		X			X			X
Blood for Avelumab ADA[4]	X				X						
12-Lead ECG collection[5]	X	X			X			X			

ADA=anti-drug antibody; AM=morning; ECG=electrocardiogram; PK=pharmacokinetic

Table 2 provides guidance specifically for subset of patients in Cohorts A1 and A3 who will undergo serial PK collection and matching ECG measurements, and includes required assessments for Cycle 1 and Cycle 2 only**. For assessments conducted in the remainder of patients and remaining cycles/visits beyond Cycle 2, see Schedule of Activities Table 1.**

The assessment schedule is to be used with the following administration schedule for Cycle 2 Day 1: administration of pemetrexed IV over 10 min, followed by carboplatin IV over 1 hr starting 20 min after end of pemetrexed infusion, followed by avelumab IV over 1 hr starting 30 min after end of carboplatin infusion. If an infusion time is increased for a given agent, end of infusion and subsequent post-dose PK samples (and time-matched ECGs, if applicable) for that drug only should shift accordingly.

1. **Blood for Pemetrexed Pharmacokinetics:** Blood samples (2 mL whole blood at each specified time point) will be collected at pre-dose, 10 min post-start of pemetrexed infusion (ie, at the end of infusion), and at 1.5 hrs and 5.5 hrs post-start of pemetrexed infusion (corresponding to 1 hr 40 min and 5 hrs 40 min post-end of pemetrexed infusion) on Day 1 of Cycle 2; an additional sample will be collected during the Day 8 visit of Cycle 2. End of infusion PK samples for pemetrexed must be collected within 10 min post end of infusion of pemetrexed.
2. **Blood for Carboplatin Pharmacokinetics:** Blood samples (3 mL whole blood at each specified time point) will be collected at pre-dose, 1 hr post-start of carboplatin infusion (ie, at the end of infusion), and at 2.5 hrs and 5 hrs post-start of carboplatin infusion (corresponding to 1.5 hrs and 4 hrs post-end of carboplatin infusion) on Day 1 of Cycle 2; an additional sample will be collected during the Day 8 visit of Cycle 2. End of infusion PK samples for carboplatin must be collected within 10 min post end of infusion of carboplatin.
3. **Blood for Avelumab Pharmacokinetics:** In all patients, blood samples (3.5 mL whole blood at each specified time point) will be collected at pre-dose and 1 hr post-start of avelumab infusion (ie, at the end of avelumab infusion) on Day 1 of Cycle 1 and Cycle 2; an additional sample will be collected during the Day 15 visit of Cycle 1 and 2. End of infusion PK samples must be collected within 30 min post end of avelumab infusion (after completion of triplicate ECG).
4. **Blood for Anti-Avelumab Antibodies (Anti-Drug Antibodies: ADA):** In all patients, blood samples (3.5 mL whole blood at each specified time point) for avelumab immunogenicity testing will be collected pre-dose on Day 1 of Cycles 1 and 2.

5. **12-Lead Electrocardiogram (ECG) Time-Matched with PK:** On-treatment triplicate ECGs will be performed before (pre-dose) administration of any study drug and 1 hr post-start of avelumab infusion (ie, at the end of avelumab infusion) for all patients on Day 1 of Cycles 1 and 2. All pre-dose ECGs are to be collected prior to administration of any study drug (along with any pre-dose PK or ADA samples). At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When the ECG measurements coincide with blood sample draws for PK, the PK sample should be taken as close as possible to the end of infusion time for the investigational product, with an allowance of ±10 minutes. ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.
6. PK samples on Day 8 and Day 15 may be collected at any time during the visit.

Table 3. SCHEDULE OF ACTIVITIES: UC – Avelumab + Gemcitabine/Cisplatin, Cohorts A2 and A4

		On-Treatment: One cycle = 21 days				Post-Treatment		
	Screening	Immunotherapy + Chemotherapy			Immunotherapy			
Protocol Activities[1]	Within 28 Days Prior to Enrollment	Gemcitabine/Cisplatin/Avelumab			Avelumab	End of Treatment +7 days[22]	Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]	Long-Term Follow-up (Every 12 weeks ±14 days)[24]
		Day 1 ±2 days[39]	Day 8 ±2 days	Day 15 ±2 days Cycles 1-3 only	Day 1 of each cycle ±2 days			
Clinical Assessments								
Informed Consent[2]	X							
Medical/Oncological History[3]	X							
Baseline Signs/Symptoms[4]	X							
Physical Examination[5]	X	X	X		X	X	X	
ECOG Performance Status[6]	X	X	X		X	X	X (Day 30 only)	
Vital Signs and Weight[7]	X	X	X		X	X	X	
Contraceptive Check[8]	X	X	X		X	X	X	
Laboratory Studies								
Hematology[9]	X	X	X	X	X	X	X	
Blood Chemistry[9]	X	X	X	X	X	X	X	
Coagulation[9]	X	X			X	X	X	
Thyroid function/ACTH[10]		Day 1 of Cycle 1, Cycle 4, and then every 3 cycles thereafter				X	X	
Urinalysis[11]	X	If clinically indicated				X		
Pregnancy Test[12]	X	X	X		X	X	X	
HBV and HCV Tests[13]	X							
12-Lead ECG[14]	X	X			If clinically indicated			
Enrollment and Study Treatment								
Enrollment[15]		X						
Gemcitabine Administration[16]		X	X					
Cisplatin Administration[16]		X						
Avelumab Administration[17]		X			X			

Table 3 SCHEDULE OF ACTIVITIES: UC – Avelumab + Gemcitabine/Cisplatin, Cohorts A2 and A4 (continued)

		On-Treatment: One cycle = 21 days				Post-Treatment		
	Screening	Immunotherapy + Chemotherapy			Immunotherapy			
Protocol Activities[1]	**Within 28 Days Prior to Enrollment**	**Gemcitabine/Cisplatin/Avelumab**			**Avelumab**	**End of Treatment +7 days[22]**	**Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]**	**Long-Term Follow-up (Every 12 weeks ±14 days)[24]**
		Day 1 ±2 days[39]	**Day 8 ±2 days**	**Day 15 ±2 days Cycles 1-3 only**	**Day 1 of each cycle ±2 days**			
Disease Assessments								
Tumor Assessments/Scans[18]	X	Cycle 3 Day 1 (±2 days), then every 6 weeks (±2 days). After 1 year from first dose of study drug, every 12 weeks (±14 days) until progressive disease regardless of initiation of new anti-cancer therapy.						
Other Clinical Assessments								
Serious and Non-serious Adverse Event Monitoring[19]	X	Monitored and recorded throughout treatment				X	X	
Concomitant Treatments[20]	X	Monitored and recorded throughout treatment				X	X	
Short- and Long-Term Follow-up After Last Dose of Study Treatment								
Subsequent Anti-Cancer Treatments[21]							X	X
Short-term Follow-up Assessments[23]							X	
Long-term/Survival Assessment[24]							X	X
Samples for Pharmacodynamic, Pharmacokinetic, CCI Analyses								
De Novo Tumor Biopsy or Archival FFPE Tumor Tissue Block[25]	X							
On-Treatment Tumor Biopsy[26]			X Cycle 2 only (–7days to +2 days)					
End of Treatment Tumor Biopsy[27]						X		
Avelumab PK[28]		X (select cycles)		X	X (select cycles)			
Anti-Avelumab Antibodies (ADA)[29]		X (select cycles)			X (select cycles)	X		
Gemcitabine PK[30]		X (Cycle 2 subset patients)						

Table 3 SCHEDULE OF ACTIVITIES: UC – Avelumab + Gemcitabine/Cisplatin, Cohorts A2 and A4 (continued)

		On-Treatment: One cycle = 21 days				Post-Treatment		
	Screening	Immunotherapy + Chemotherapy			Immunotherapy			
Protocol Activities[1]	Within 28 Days Prior to Enrollment	Gemcitabine/Cisplatin/Avelumab			Avelumab	End of Treatment +7 days[22]	Short-Term Follow-up (Day After Last Dose 30±3, 60±3, 90±3)[23]	Long-Term Follow-up (Every 12 weeks ±14 days)[24]
		Day 1 ±2 days[39]	Day 8 ±2 days	Day 15 ±2 days Cycles 1-3 only	Day 1 of each cycle ±2 days			
Cisplatin PK[31]		X (Cycle 2 subset patients)	X (Cycle 2 subset patients)					
CCI [redacted]								

ACTH=adrenocorticotropic hormone; BID=twice daily; ECG=electrocardiogram; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; FFPE=formalin-fixed, paraffin-embedded; HBV=Hepatitis B virus; HCV=Hepatitis C virus; PK=pharmacokinetics; CCI [redacted]

Footnotes for Table 3 SCHEDULE OF ACTIVITIES

1. **Protocol Activities:** All assessments should be performed prior to study treatment dosing unless otherwise indicated. Acceptable time windows for performing each assessment are provided in the column headers.
2. **Informed Consent:** Must be obtained prior to the patient undergoing any study-specific procedure.
3. **Medical/Oncological History:** Both medical and oncological histories are to be collected within 28 days prior to first dose of study treatment. Medical history should include history of other disease (active or resolved) as well as concomitant illnesses. Oncological history should include information on prior regimens (including dosing and duration of therapy, best overall response, and disease recurrence/progression date), surgery, and radiation therapy.
4. **Baseline Signs/Symptoms:** To be recorded on the Medical History CRF form. Patients will be asked about any signs and symptoms experienced within the 14 days prior to signing the informed consent document. After signing the informed consent document, any new or worsening conditions since baseline should be reported on the AE CRF.
5. **Physical Examination:** Includes an examination of major body systems (height included at screening only).
6. **ECOG Performance Status:** ECOG performance scale may be found in Appendix 2. Determination of ECOG Performance Status will continue through the 30-day Follow-Up visit unless the patient has started on a new anti-cancer therapy.
7. **Vital Signs and Weight:** See Section 7.1.
8. **Contraception Check:** See Section 4.3 and Section 7.1.2.
9. **Coagulation, Hematology, and Blood Chemistry (full panel)**: Cycle 1 Day 1 tests do not need to be repeated if they have been conducted in the prior 3 days and data are available for review. Full hematology and full clinical chemistry tests must be performed. Full hematology panel as well as AST, ALT, and creatinine results must be reviewed by medically-qualified study personnel prior to each administration of study drug. Results from all other laboratory assessments are not required to be reviewed prior to study drug dosing, unless there are signs or symptoms to suggest an underlying lab abnormality. However, all lab results should be reviewed as soon as they are available. Laboratory tests may be performed up to 3 days prior to each scheduled visit so that results will be available for review. All lab results should be reviewed as soon as they are available. Required tests are listed in Section 7.1.4. Full chemistry panel is required at Screening, Day 1, Day 8, and Day 15 of Cycles 1 through 3; Day 1 of every subsequent cycle; End of Treatment; and at the 30-day follow-up visit. Core chemistry panel (required tests are listed in Section 7.1.4) is required at Follow-Up Day 60 and Day 90. Coagulation and hematology are required as noted in this table. If the patient permanently discontinues chemotherapy before Cycle 4, but continues on avelumab and/or other anti-cancer immunotherapies in future portions of the study, then chemistry and hematology samples should be obtained at Day 1 of subsequent cycles. Any test may also be performed when clinically indicated. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.
10. **Thyroid Function/ACTH Tests**. Additional tests should be performed when clinically indicated. See Section 7.1.4.
11. **Urinalysis**: Required only at Screening and End of Treatment. To be performed if clinically indicated at other time points. Required tests are listed in Section 7.1.4.
12. **Serum/Urine Pregnancy Test:** Results of the pregnancy test must be available prior to each study treatment dosing. See Section 7.1.1.
13. **HBV and HCV Tests:** HBV surface antigen and anti-HCV antibody will be performed at Screening. HCV RNA will be performed if anti-HCV antibody test is positive (Section 7.1.4, Table 14).

14. **12-Lead Electrocardiogram (ECG):** All patients require triplicate ECG measurements at screening and on treatment. On treatment triplicate ECGs will be performed on Day 1 of Cycles 1 to 3, before (pre-dose) and at the end of avelumab infusion for all patients. See Table 4 for ECG monitoring of subset of patients undergoing serial PK collection in Cohorts A2 and A4. See Section 7.1.6.
15. **Enrollment:** Study treatment must be initiated preferably on the day of enrollment, but no later than 3 days after enrollment. Patients meeting all entry criteria will be registered and enrolled using the Interactive Response Technology system. See Section 5.1.
16. **Gemcitabine/cisplatin:** Gemcitabine 1000 mg/m^2 will be administered IV on Day 1 and Day 8 of each 21-day cycle. Cisplatin 70 mg/m^2 will be administered IV on Day 1 of the 21-day cycle. On visits when both chemotherapy and avelumab are infused (Day 1 of each 21-day cycle), chemotherapy will be infused before avelumab. Patients will receive any premedications as per local guidance. See Section 5.4.3. See Section 5.2 for guidance on treatment duration.
17. **Avelumab Administration:** Avelumab 800 mg will be administered Q3W (Day 1 of each 21-day cycle). 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 intravenous infusion on Day 1 of each 21-day cycle. On visits when both chemotherapy and avelumab are infused (Day 1 of each 21-day cycle), avelumab will be infused *after* chemotherapy but within 30 minutes (+20-minute time window if needed) of the end of the chemotherapy infusion, see Section 5.4.3. See Section 5.4.1.3 for guidance on required premedication for avelumab infusion. See Section 5.2 for guidance on treatment duration.
18. **Tumor Assessments:** For patients with UC, tumor assessments by CT or MRI scans will include chest, abdomen, and pelvis CT or MRI scans at all time points. Baseline scans must be performed within 28 days prior to first dose of study drug. See Section 7.6 for complete information.
19. **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) v 4.03. See Section 8.1.4 for guidance on the time period for collecting and reporting AE and SAEs. If a patient begins a new anti-cancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the active collection period.
20. **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, see Section 5.7.
21. **Subsequent Anti-Cancer Treatments:** These treatments will be documented and recorded for patients who discontinue all study treatments and continue in the Short –term and Long-Term Survival periods of the study.
22. **End of Treatment (discontinuation of all study drugs for any reason):** Obtain these assessments if not completed in the prior 7 days.
23. **Short-Term Follow-Up after Last Dose of Study Treatment:** All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first. See Section 6.3 for guidance on tumor assessment during Short-term Follow-up.
24. **Long-Term Follow-up (Survival):** Following completion of the end of treatment visit, all patients will be followed for survival and subsequent anti-cancer treatments every 12 weeks (±14 days) until death, end of the study, or patient withdrawal of consent, whichever comes first. See Section 6.3 for guidance on tumor assessment during Long-term Follow-up.
25. ***De Novo* Tumor Biopsy and Archival FFPE Tumor Tissue Block:** See Section 6.1.1.
26. **On-Treatment Tumor Biopsy:** See Section 6.1.1.
27. **At Progression Tumor Biopsy:** An optional *de novo* tumor sample is encouraged to be collected at End of Treatment if a patient discontinues due to disease progression. See Section 6.1.1.

28. **Blood for Avelumab Pharmacokinetics:** Blood samples (3.5 mL whole blood at each specified time point) will be collected from all patients in the study at pre-dose and 1 hour post-start of avelumab infusion (ie, at the end of infusion) on Day 1 of Cycles 1, 2, 3, 6, 10, and 14; an additional sample will be collected during the Day 15 visit of Cycle 1, 2, and 3. See Section 7.2.1.
29. **Blood for Anti-Avelumab Antibodies (Anti-Drug Antibodies: ADA):** Blood samples (3.5 mL whole blood at each specified time point) for avelumab immunogenicity testing will be collected from all patients pre-dose on Day 1 of Cycles 1, 2, 3, 6, 10, and 14, and at End of Treatment, see Section 7.3.
30. **Blood for Gemcitabine Pharmacokinetics (only in subset of patients undergoing serial PK):** See Table 4 and Section 7.2.2.3.
31. **Blood for Cisplatin Pharmacokinetics (only in subset of patients undergoing serial PK):** See Table 4 and Section 7.2.2.4.

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39. The visit window for Day 1 visits post Cycle 1 during study treatment is ±2 days.

Table 4. PK and ECG ASSESSMENTS (Only for Subset of Patients Undergoing Serial PK): UC – Avelumab + Gemcitabine/Cisplatin, Cohorts A2 and A4

	Cycle 1				Cycle 2							
	Day 1		Day 15		Day 1						Day 8[6]	Day 15[6]
	Time after start of gemcitabine infusion (hr)				Time after start of gemcitabine infusion (hr)							
	Pre-dose	3.5			Pre-dose	0.5	1.0	2.0	3.5	6.0		
All Cohorts:												
Blood for Gemcitabine PK[1]					X	X	X	X				
Blood for Cisplatin PK[2]					X			X	X	X	X	
Blood for Avelumab PK[3]	X	X	X		X				X			X
Blood for Avelumab ADA[4]	X				X							
12-Lead ECG collection[5]	X	X			X				X			

ADA=anti-drug antibody; AM=morning; ECG=electrocardiogram; PK=pharmacokinetic

Table 4 provides guidance specifically for subset of patients in Cohorts A2 and A4 who will undergo serial PK collection and matching ECG measurements and includes required assessments for Cycle 1 and Cycle 2 only. **For assessments conducted in the remainder of patients and remaining cycles/visits beyond Cycle 2, see Schedule of Activities Table 3.**

This assessment schedule is to be used with the following administration schedule for Cycle 2 Day 1: administration of gemcitabine IV over 30 min, followed by administration of cisplatin IV over 1 hour starting 30 min after end of gemcitabine infusion, followed by avelumab IV over 1 hour starting 30 min after end of cisplatin infusion. If an infusion time is increased for a given agent, end of infusion and subsequent post-dose PK samples (and time-matched ECGs, if applicable) for that drug only should shift accordingly.

1. **Blood for Gemcitabine Pharmacokinetics:** Blood samples (3 mL whole blood at each specified time point) will be collected at pre-dose, 0.5 hr (30 min) post-start of infusion (ie, at the end of infusion), and at 1 hr and 2 hrs post-start of gemcitabine infusion (corresponding to 0.5 hr (30 min) and 1.5 hrs post-end of infusion) on Day 1 of Cycle 2. End of infusion PK samples for gemcitabine must be collected within 10 min post end of infusion of gemcitabine.
2. **Blood for Cisplatin Pharmacokinetics:** Blood samples (3 mL whole blood at each specified time point) will be collected at pre-dose, 1 hr post-start of infusion (ie, at the end of infusion), and at 2.5 hrs and 5 hrs post-start of cisplatin infusion (corresponding to 1.5 hrs and 4 hrs post-end of infusion) on Day 1 of Cycle 2; an additional sample will be collected during the Day 8 visit of Cycle 2. End of infusion PK samples for cisplatin must be collected within 10 min post end of infusion of cisplatin.
3. **Blood for Avelumab Pharmacokinetics:** In all patients, blood samples (3.5 mL whole blood at each specified time point) will be collected at pre-dose and 1 hr post-start of avelumab infusion (ie, at the end of avelumab infusion) on Day 1 of Cycles 1 and 2; an additional sample will be collected during the Day 15 visit of Cycle 1 and Cycle 2. End of infusion PK samples must be collected within 30 min post end of infusion of avelumab (after completion of triplicate ECG).
4. **Blood for Anti-Avelumab Antibodies (Anti-Drug Antibodies: ADA):** In all patients, blood samples (3.5 mL whole blood at each specified time point) for avelumab immunogenicity testing will be collected pre-dose on Day 1 of Cycles 1 and 2.

5. **12-Lead Electrocardiogram (ECG) Time-Matched with PK:** On-treatment triplicate ECGs will be performed before (pre-dose) administration of any study drug and 1 hr post-start of avelumab infusion (ie, at the end of avelumab infusion) for all patients on Day 1 of Cycles 1 and 2. All pre-dose ECGs are to be collected prior to administration of any study drug (along with any pre-dose PK or ADA samples). At each time point, three (3) consecutive 12-lead ECGs (triplicates) will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When the ECG measurements coincide with blood sample draws for PK, the PK sample should be taken as close as possible to the end of infusion time for the investigational product, with an allowance of ±10 minutes. ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time.
6. PK samples on Day 8 and Day 15 may be collected at any time during the visit.

1. INTRODUCTION

This is a Phase 1b/2, open-label, multi-center, safety, clinical activity, pharmacokinetic (PK), and pharmacodynamic (PD) study of avelumab (MSB0010718C), a programmed death-ligand 1 (PD-L1) monoclonal antibody (mAb), in combination with standard-of-care chemotherapy with or without other anti-cancer immunotherapies as first-line therapy in patients with locally advanced or metastatic solid tumors. Avelumab is expected to increase the effectiveness of antitumor T cells by preventing inhibition of T cell activation. Combination of avelumab with agents that enhance the immune response by different mechanisms would be expected to lead to an increase in antitumor activity over that seen with avelumab alone. Initially, avelumab will be evaluated in combination with standard-of-care chemotherapy in patients with advanced malignancies. In portions of the study to be added in the future, additional combinations of avelumab plus standard-of-care chemotherapy with or without other anti-cancer immunotherapy agent(s), other than other anti-PD-1/PD-L1 mAb, may be incorporated via protocol amendment based on emerging preclinical and clinical data. See Section 3.1 for additional details. For the United Kingdom (UK) and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

1.1. Indication

This study will investigate avelumab in combination with standard-of-care chemotherapy with or without other anti-cancer immunotherapies as first-line therapy for patients with advanced or metastatic solid tumors. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

1.2. Background and Rationale

1.2.1. Avelumab

Avelumab selectively binds to 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.[1] For complete details of the in vitro and nonclinical studies, refer to the avelumab Investigator's Brochure (IB).[2]

1.2.1.1. Avelumab Clinical Experience

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

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

The safety profile of avelumab administered intravenously (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in MCC (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types.

As of 09 June 2016, a total of 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg Q2W, 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.

The dose expansion phase of study EMR100070-001 included patients with NSCLC, gastric cancer, breast cancer, colorectal cancer, castration resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, UC, ovarian cancer, RCC, and SCCHN. Study EMR100070-003 Part A was conducted in patients with MCC.

A summary of pooled safety data from patients treated at 10 mg/kg Q2W in studies EMR100070- 001 and EMR100070-003 (N=1738) is provided here.

Treatment-emergent adverse events (TEAEs) were observed in 1697 (97.6%) patients, with the most frequent (≥10%) being fatigue (32.4%), nausea (25.1%), diarrhea (18.9%), constipation (18.4%), decreased appetite (18.4%), infusion related reaction (17.1%), weight decreased (16.6%), vomiting (16.2%), anemia (14.9%), abdominal pain (14.4%), cough (13.8%), pyrexia (13.6%), dyspnea (13.2%), edema peripheral (11.9%), back pain (11.8%), and arthralgia (10.4%).

Treatment-related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (≥5%) 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%).

A total of 177 patients (10.2%) experienced Grade ≥3 treatment-related TEAEs, and the most frequent (≥0.5%) were fatigue (1.0%), lipase increased (1.0%), gamma-glutamyl transferase (GGT) increased (0.6%), infusion related reaction (IRR, 0.6%), and aspartate transaminase (AST) increased (0.5%).

A total of 777 (44.7%) patients had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 108 (6.2%) patients, with the most frequent (≥0.2%) being IRR (0.9%), pneumonitis (0.6%), pyrexia (0.3%), adrenal insufficiency (0.3%), and hypothyroidism, diarrhea, vomiting, autoimmune disorder, autoimmune hepatitis, transaminases increased, dyspnea, and colitis (0.2% each).

There were 911 deaths (52.4%) in the pooled safety data set. The majority of deaths were due to progressive disease (744, 42.8%). There were 59 (3.4%) deaths attributed to TEAEs not related to trial treatment, and 4 deaths (0.2%) attributed to a treatment-related TEAE by the Investigator and which occurred up to 30 days after the last dose of avelumab: pneumonitis (1 case), acute liver failure (1 case), respiratory distress (in the context of sepsis) (1 case), and autoimmune hepatitis with hepatic failure (1 case). In addition, 1 patient died with acute respiratory failure (in the context of lung cancer progression) considered related to avelumab by the Investigator 37 days after the last dose of avelumab. The cause of death was marked as "other" or "unknown" in 17 (1.0%) and 83 (4.8%) of cases, respectively.

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment-related TEAEs. The most frequent treatment related TEAEs leading to treatment discontinuation were infusion related reaction (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, alanine aminotransferase (ALT) increased, blood creatinine phosphokinase (CPK) increased, lipase increased, arthralgia, and pneumonitis (0.2% each).

Immune-related adverse events (irAEs): in the pooled safety data (N=1738), a total of 247 patients (14.2%) experienced irAEs, defined as adverse events requiring use of corticosteroids (and/or hormonal therapy for endocrinopathies), and no clear alternate etiology. The median time to first onset of an irAE was 11.7 weeks. The most frequent irAEs were thyroid disorders including hypothyroidism (5.2%), hyperthyroidism (0.4%) and thyroiditis (0.2%), immune-related rash (5.2%), immune-related colitis (1.5%), immune-related pneumonitis (1.2%), immune-related hepatitis (0.9%), adrenal insufficiency (0.5%) and immune-related myositis (0.5%). In addition, irAEs reported in 0.1% of patients in the pooled safety dataset included: type 1 diabetes mellitus, immune-related nephritis/renal dysfunction, hypopituitarism, uveitis and Guillain-Barre Syndrome. The majority of irAEs were Grade 1 or Grade 2 in severity, with 39 (2.2%) being of Grade ≥3 severity. Fatal outcome was reported in 1 patient (0.1%) with immune-related pneumonitis, and 2 patients (0.1%) with immune-related hepatitis. Other relevant irAEs reported with avelumab outside the pooled safety dataset included 1 case of fatal immune-related myocarditis in Study B9991002 (avelumab in combination with axitinib for RCC), 1 case of non-fatal immune-related myocarditis in the 20 mg/kg cohort of the dose escalation phase of Study EMR100070-001, and 2 patients with non-fatal graft versus host disease (GVHD) in Study B9991007 (avelumab in patients with classical Hodgkin's lymphoma).

Infusion-related reactions (IRRs): a total of 439 patients (25.3%) experienced at least 1 IRR, defined as a TEAE coded under the preferred terms (PTs) of IRR, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common PTs that met the definition for an IRR included: IRR (17.0%), chills (5.4%), and pyrexia (3.6%). Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 IRRs occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥3 IRRs occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had >3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an IRR.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[2]

Immunogenicity of Avelumab in Humans: Immunogenicity assessment included all patients from Studies EMR100070-001 and EMR100070-003 treated with 10 mg/kg of avelumab Q2W who had at least one valid anti-drug antibody (ADA) result as of the data cut-off date of 09 June 2016. Of the 1738 patients treated with avelumab, 1558 were evaluable for treatment-emergent ADAs and 64 (4.1%) tested positive. Titers were generally low across ADA ever-positive patients, with no clear relationship between the duration of immunogenicity response and the maximum observed titer. Current data suggest there is no clinically meaningful impact of ADA positivity on PK, efficacy, or safety.

1.2.1.2. Clinical Experience in Patients with Locally Advanced or Metastatic NSCLC

Avelumab has been evaluated in first-line NSCLC patients in a tumor-specific expansion cohort of Study EMR 100070-001. As of 19 February 2016, 156 patients with advanced NSCLC not previously treated systemically for metastatic or recurrent disease, without an activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, and not preselected for PD-L1 expression were enrolled in this cohort.

The objective response rate (ORR) based on confirmed and unconfirmed responses was 22.4% (35 [2 complete response {CR} and 33 partial response {PR}] of 156 patients [95% confidence interval (CI) 16.2-29.8%]). In 24 of 35 responders (68.6%), the responses were ongoing at the time of the data cutoff. The onset of the response was rapid, with 28 of 35 responders (80%) having their first documented response by the first or second tumor assessments (Weeks 6 and 12, respectively). An additional 67 patients (42.9%) had a best overall response (BOR) of stable disease (SD). The median progression-free survival (PFS) as per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 was 17.6 weeks (95% CI: 11.6, 23.6). The PFS rate at 24 weeks by Kaplan-Meier estimate was 37.2% (95% CI 28.6-45.7%).[2]

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

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

This approval was based on data from 2 cohorts of Study EMR 100070-001 into which 242 patients were enrolled. In the pooled group of 226 patients who had at least 13 weeks follow-up, the confirmed ORR by Independent Endpoint Review Committee (IERC) was 13.3% (30 [9 CR and 21 PR] of 226 patients [95% CI 9.1-18.4%]). The median time to response was 2.0 months (range: 1.3 to 11.0). Among the total 30 responding patients, 22 patients (73%) had ongoing responses of 6 months or longer and 4 patients (13%) had ongoing responses of 12 months or longer.

In the pooled group of 161 patients who had at least 6 months follow-up, the confirmed ORR by IERC was 16.1% (26 [9 CR and 17 PR] of 161 patients [95% CI 10.8-22.8%]). As for those patients who had at least 13 weeks follow-up, the median time to response was 2.0 months (range: 1.3 to 11.0). Among the total 26 responding patients, 22 patients (85%) had ongoing responses of 6 months or longer and 4 patients (15%) had ongoing responses of 12 months or longer.[3]

1.2.1.4. Pharmacokinetics of Avelumab in Humans

Available PK data from EMR100070-001 show that the concentration at the end of the dosing interval (C_{trough}) increased more than proportionally to dose between 1 to 10 mg/kg and proportionally to dose for doses above 10 mg/kg. The terminal half-life ($t_{1/2}$) also increased with dose; however, the geometric mean values for $t_{1/2}$ were similar for the 10 mg/kg and 20 mg/kg dose levels, at 94.6 hours (3.96 days) and 99.1 hours (4.1 days), respectively. This PK characteristic suggests that target mediated drug disposition is involved in the clearance of avelumab and that high PD-L1 target receptor occupancy (TO) is likely achieved throughout the dosing interval at doses of 10 mg/kg and 20 mg/kg given every 2 weeks.

The 10 mg/kg dose Q2W achieved high TO (mean TO >90%) of PD-L1 in peripheral blood mononuclear cells (PBMC) during the entire dosing interval, as determined from ex vivo studies. Based on the in vitro TO data and the observed trough serum avelumab levels in the dose escalation cohorts of Study EMR100070-001, TO was predicted to reach or exceed 95% throughout the entire dosing interval in more patients in the 10 mg/kg dose group than in the 3 mg/kg dose group.

Avelumab is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by small molecule drugs that are cytochrome P450 (CYP) enzyme modulators or by transporter modulators. Population PK analysis did not show any meaningful effects on clearance of avelumab from premedication with acetaminophen (paracetamol) or diphenhydramine, nor from concomitant medication

with ibuprofen, acetylsalicylic acid, opioids, corticosteroids, or biological therapies evaluated to date.

Complete information for avelumab may be found in the SRSD, which for this study is the avelumab IB.[2]

1.2.2. Chemotherapy

For the specified chemotherapy agents used in this study, please refer to the product local label for clinical experience and pharmacokinetics information. Complete information for carboplatin, cisplatin, pemetrexed and gemcitabine may be found in the single reference safety documents (which for this study are the Paraplatin®, Platinol®, Alimta®, and Gemzar® United States Prescribing Information [USPI], respectively).[38,39,41,42]

1.2.3. Study Rationale

1.2.3.1. Rationale for Combining Avelumab with Chemotherapy

There are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[4,5] Chemotherapy has been shown to have immunostimulatory properties via its ability to promote the release of neoantigens and to enhance antigen uptake and presentation via the process of immunogenic cell death, hence leading to an increase in immune priming against the tumor. In addition, a number of chemotherapies have been shown to alter the immunogenicity of tumor cells both at the cell intrinsic level, through modulation of cell surface proteins like major histocompatibility complex (MHC), and also at the cell extrinsic level, though depletion of suppressive elements within the microenvironment such as regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs).[6-9] Cisplatin has been shown in preclinical models to lead to increased intratumoral CD8 T cell cytotoxicity and to increased antitumor activity in combination with checkpoint blockade.[10] Platinum-based chemotherapy regimens in general have been suggested to promote immune priming, as evidenced by increased MHC class I and PD-L1 expression and increased CD8 T-cell infiltration into tumors post-treatment.[11] In addition, gemcitabine has been shown in preclinical models to reduce the levels of suppressive MDSCs within the tumor,[12] and has been shown in patients to reduce the circulating levels of both MDSCs and tumor growth factor (TGF)-β, which can be a suppressive signal for T cells.[13] The combination of avelumab with several chemotherapies including gemcitabine, oxaliplatin, and 5-fluorouracil, showed improved antitumor activity relative to single-agent chemotherapy in preclinical studies.[2]

Several immune checkpoint inhibitors have been combined with chemotherapy agents. Single-arm studies investigating the combination of PD-1 blockers (pembrolizumab, nivolumab) as well as a PD-L1 blocker (atezolizumab) with platinum doublet chemotherapy demonstrated acceptable safety profiles with early evidence of clinical activity which appears to be higher than expected for platinum doublet therapy alone, especially for atezolizumab.[14-18] Of particular relevance to Study B9991023 are results from studies of PD-1/PD-L1 inhibitors plus platinum doublet chemotherapy as first-line therapy in patients with advanced or metastatic NSCLC. In one randomized, open-label, Phase 2 cohort of the KEYNOTE-021 study,[27] the combination of carboplatin and pemetrexed with or without

pembrolizumab was evaluated in patients with advanced non-squamous NSCLC. A significant increase in ORR (55%; 95% CI 42-68%) was noted for the triplet therapy relative to the ORR for chemotherapy alone (29%; 95% CI 18-41%). In addition, median PFS for patients treated with the triplet (13.0 months; (95% CI 8.3-not reached)) was significantly longer than that for chemotherapy-treated patients (8.9 months; (95% CI 4.4-10.3)). The PFS hazard ratio (HR) was 0.53 (95% CI 0.31-0.91; p=0.010). Results from OS data were not yet mature at the time of publication. In this patient population, the observed increase in ORR for patients treated with the triplet as compared to chemotherapy-treated patients was demonstrated along with PFS prolongation, suggesting that this magnitude of ORR increase would translate into a clinically meaningful and statistically significant difference in a time-to-event efficacy endpoint. Based on data from the KEYNOTE-021 study, on 10 May 2017, the FDA approved pembrolizumab in combination with carboplatin and pemetrexed for the first-line treatment of patients with metastatic non-squamous NSCLC, irrespective of PD-L1 expression.[52]

In independent cohorts of a separate study,[19,20] nivolumab alone or in combination with 3 different platinum doublets was tested as first-line therapy in patients with advanced NSCLC. Improvements in both ORR and median PFS were noted for nivolumab in combination with gemcitabine/cisplatin, pemetrexed/cisplatin, or paclitaxel/carboplatin over those seen with nivolumab alone. Notable ORRs were also observed when atezolizumab was combined with pemetrexed/carboplatin, carboplatin/paclitaxel, or carboplatin/nab-paclitaxel as first-line therapy for patients with advanced NSCLC.[21]

Overall these clinical and preclinical data are supportive of the potential for increased antitumor activity through the combination of chemotherapy and avelumab. Avelumab is currently under investigation in 2 Phase 3 ovarian cancer trials in combination with carboplatin/paclitaxel in one trial and with pegylated liposomal doxorubicin in the second trial. While results from both studies are blinded to the Pfizer teams, early safety data have been reviewed by external data monitoring committees and both studies have been approved to continue.

1.2.3.2. Rationale for the Tumor Types Under Evaluation

The specific tumor types to be enrolled in Group A were selected because:

- These tumor types are responsive to chemotherapy, which currently is first-line standard-of-care for these indications;
- Avelumab has shown preliminary evidence of clinical activity as monotherapy in the specific tumor types (NSCLC[2] and UC;[3] see Section 1.2.1.2 and Section 1.2.1.3 respectively).

1.2.3.3. Rationale for the Chemotherapy Doublets to be Evaluated in this Study

Chemotherapy doublets selected for use in Group A represent standard-of-care first-line therapies for the 2 tumor types that will initially be evaluated in this study.

The doublet carboplatin plus pemetrexed will be used to treat patients with advanced or metastatic non-squamous NSCLC. In 2005, Scagliotti et al[24] reported the results of a multicenter, randomized, Phase 2 trial of pemetrexed in combination with either oxaliplatin or carboplatin as first-line treatment of patients with advanced NSCLC. The intent of this study was to identify new treatment regimens that provided the same level of efficacy as that seen with cisplatin chemotherapy doublets, but with an improved toxicity profile. The ORRs were 26.8% (95% CI 14.2-42.9%) for patients treated with pemetrexed/oxaliplatin and 31.6% (95% CI 17.5-48.7%) for patients treated with pemetrexed/carboplatin. These rates were similar to those seen in 4 randomized Phase 3 trials evaluating the following platinum doublets: paclitaxel and cisplatin; gemcitabine and cisplatin; docetaxel and cisplatin; paclitaxel and carboplatin; vinorelbine and cisplatin; and docetaxel and carboplatin. In addition, the oxaliplatin/pemetrexed and carboplatin/pemetrexed doublets had improved safety profiles relative to those from other platinum-based doublets – for both hematologic and non-hematologic toxicities.[22-25] These results indicated a favorable risk/benefit profile for these 2 doublets. In 2016, Gadgeel et al[26] published results from early cohorts of KEYNOTE-021 in which the PD-1 inhibitor pembrolizumab was combined with 3 different chemotherapy regimens (carboplatin/paclitaxel, carboplatin/paclitaxel/bevacizumab, and pemetrexed/carboplatin) as first-line therapy for patients with advanced NSCLC. The combination of pemetrexed/carboplatin demonstrated the most promising activity. Based on these results and as part of KEYNOTE-021, Langer et al[27] evaluated the combination of pemetrexed/carboplatin plus pembrolizumab in a larger randomized cohort of patients with advanced non-squamous NSCLC and observed an increase in ORR and longer PFS for the triplet therapy compared to chemotherapy alone (See Section 1.2.3.1). Given these cumulative results, carboplatin/pemetrexed was selected for first-line treatment of patients with non-squamous NSCLC enrolled in this study.

Gemcitabine/cisplatin has long been established as the standard first-line chemotherapy regimen for those patients with advanced or metastatic UC who are eligible to receive this combination.[32,33] Comparison of gemcitabine/cisplatin to methotrexate/vinblastine/ doxorubicin/cisplatin (MVAC) revealed similar OS, time to PD, time to treatment failure, and response rate for the 2 regimens. The safety profile and tolerability of the gemcitabine/cisplatin doublet was better than those for the MVAC regimen resulting in adoption of the doublet as standard of care first-line therapy. In the von der Maase studies,[32,33] gemcitabine/cisplatin was dosed on a 4-week cycle with gemcitabine administered on Day 1, 8, and 15 and cisplatin administered on Day 2. Gemcitabine dosing, however, was associated with a high rate of hematologic toxicity. In an effort to determine if a 3-week cycle of gemcitabine dosed on Day 1 and 8 and cisplatin on Day 2 would be feasible, Als et al[34] conducted a retrospective analysis of patients with advanced UC who had been treated with either the standard 4-week cycle or a modified 3-week cycle. There was no statistical difference in OS between the two dosing schedules (HR=1.15, 95% CI 0.83 to 1.59, p=0.4). Response rates also were similar (3-week cycle: 59.7%; 4-week cycle 55.6%, p=0.61). The authors reported “an improved compliance profile, adequate dose intensity, and no differences in efficacy parameters for the 3-week schedule compared with the 4-week schedule”. Given these findings, patients with advanced or metastatic UC will receive gemcitabine/cisplatin on a 3-week schedule in this study.

1.2.3.4. Rationale for Investigational Product Dose

1.2.3.4.1. Avelumab

In this study, avelumab will be administered initially as an 800 mg fixed dose via 1-hour infusion Q3W in combination with chemotherapy, with or without other anti-cancer immunotherapies. After the initial avelumab dose of 800 mg Q3W in combination with chemotherapy has been evaluated and deemed safe according to the study design, avelumab 1200 mg Q3W will be explored as the next dose level.

For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

To date, avelumab has been administered at the clinically active, safe and tolerable dose of 10 mg/kg Q2W to more than 1700 patients across multiple indications. Furthermore, this 10 mg/kg Q2W avelumab dosing regimen has been approved by the US FDA for treatment of patients with MCC and UC. The preliminary data from clinical studies suggest >90% target occupancy (TO) is required for clinical benefit. Based on in vitro evidence, ≥90% TO is reached at avelumab blood concentrations >1 μg/mL; 10 mg/kg Q2W has been shown to achieve avelumab serum trough concentration (C_{trough}) >1 μg/mL.

Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for mAbs, including marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body weight-independent) dosing regimens.[35,36,37] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration. Population PK analysis was conducted based on the acquired PK data across 3 single-agent avelumab studies in patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are similar with 800 mg Q2W (fixed dose) compared to 10 mg/kg Q2W (weight-based dose), and 1600 mg Q2W compared to 20 mg/kg Q2W. Low-weight patients tended to have marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when fixed dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful.

Based on emerging data of avelumab and other PD-1 and PDL-1 inhibitors, other avelumab dosing regimens continue to be explored in various clinical studies in efforts to optimize clinical benefit in individual indications and treatment regimens, such as when used in combination with standard-of-care therapies given in a frequency which differs from Q2W. For example the Q3W dosing schedule has been evaluated in several other clinical studies of an immune checkpoint inhibitor mAb (eg, ipilimumab, nivolimumab, pembrolizumab) with platinum doublet chemotherapy; in each of these studies, the combination therapy was associated with acceptable safety.[56,57,58] A Q3W dosing schedule for avelumab will likewise be used in this study in combination with Q3W standard-of-care doublet chemotherapy

regimens as Q2W administration would result in avelumab dosing during the period of chemotherapy-induced myelosuppression nadir. Given that the safety of avelumab in patients with myelosuppression is currently unknown, a Q3W administration schedule avoids dosing of avelumab during the nadir period; the intent to avoid treating myelosuppressed patients aligns with the current avelumab dose modification guidelines for management of hematologic toxicities. The 800 mg Q3W dosing regimen (initial dose level) is still expected to provide median plasma C_{trough} >1 μg/mL at 21 days, yielding a mean TO >90% over the entire Q3W dosing interval for the majority of patients (Pfizer, data on file).

Additionally, other marketed PD-1 and PD-L1 immune checkpoint inhibitors (eg, nivolumab,[53] pembrolizumab[54] and durvalumab[55]) have demonstrated an ability to extend the dosing interval paired with an increase in dose. Such efforts are also being explored for avelumab. In two clinical studies, including the dose escalation trial, avelumab was administered at 20 mg/kg Q2W (highest tested dose) to a total of 27 patients that had shown acceptable safety profiles, and no maximum tolerated dose (MTD) was reached. For an extended dosing interval of Q3W, the projected avelumab average plasma concentration (C_{avg}) values from PK simulations following 1200 mg Q3W are similar to those observed with the 10 mg/kg Q2W dosing regimen approved in MCC and UC, and exposures following 1200 mg Q3W are projected to not exceed those observed at the highest tested dose of 20 mg/kg Q2W.

The proposed avelumab fixed dosing regimens of 800 mg Q3W and 1200 mg Q3W are expected to reach >90% TO throughout the 21-day dosing interval in the majority of patients, including when used in combination with chemotherapy or other anti-cancer immunotherapies; the 1200 mg Q3W dosing regimen is being explored additionally in this Phase 1b/2 trial since it is projected to maintain the avelumab average exposures observed with the approved dose of 10 mg/kg Q2W while extending the dosing interval for use in combination with Q3W chemotherapy regimens.

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.

The benefit-risk relationship has been carefully considered in the planning of the trial. As part of this effort, the clinical efficacy and safety profile of each of the study drugs when used individually was reviewed.

Avelumab has demonstrated clinical activity in patients with advanced solid tumors in an expansion cohort of a Phase 1 study. The available clinical safety data for single-agent avelumab dosed at 10 mg/kg Q2W in 1738 patients with advanced solid tumors demonstrate an acceptable safety profile of the compound. Most of the observed events were low grade and manageable and were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. IRRs including hypersensitivity and irAEs/autoimmune disorders have been identified as important risks for avelumab.

Although most clinical safety data are from patients treated with avelumab at 10 mg/kg Q2W, there are also limited data for patients treated at the higher dose of 20 mg/kg Q2W. Data at 20 mg/kg Q2W support a safety profile similar to that seen at 10 mg/kg Q2W. Twenty-one patients were treated with 20 mg/kg Q2W in the dose escalation portion of Study EMR100070-001, and 6 patients were treated at this dose in the Japanese Study EMR100070-002. Based on a data cut-off of 20 November 2015, for the pooled data set for EMR100070-001 and EMR100070-002 (3, 10 and 20 mg/kg Q2W), the incidence of TEAEs was similar in patients treated at doses of 10 and 20 mg/kg Q2W, with the exception of related TEAEs (90.5% at 10 mg/kg vs. 74.1% at 20 mg/kg) and related TEAEs Grade ≥3 (23.8% at 10 mg/kg vs 11.1% at 20 mg/kg) that were reported at a higher percentage in the 10 mg/kg Q2W group and related TEAEs leading to permanent discontinuation (4.8% at 10 mg/kg vs. 14.8% at 20 mg/kg) that were reported at a higher percentage in the 20 mg/kg Q2W group. Overall, irAEs were reported at similar percentages in the 10 mg/kg Q2W and 20 mg/kg Q2W dose groups (14.3% and 14.8%, respectively). The rate of infusion-related reactions was higher in the 10 mg/kg Q2W group (28.6%) than in the 20 mg/kg Q2W group (14.8%).

Respective risk mitigation measures have been implemented in all clinical studies with avelumab, including this clinical trial protocol. These include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a H1 blocker and acetaminophen prior to the first 4 avelumab infusions. All avelumab-specific guidelines apply to both the 800 mg Q3W dose and the 1200 mg Q3W dose.

There is extensive literature on the clinical utility and safety history for each of the chemotherapy agents used both individually and as part of the chemotherapy doublets planned in Study B9991023.[38,39,41,42] The combination of carboplatin with pemetrexed (Cohorts A1 and A3) and cisplatin with gemcitabine (Cohorts A2 and A4) are standard chemotherapy regimens for patients affected by non-squamous NSCLC and with cisplatin-eligible UC, respectively. These regimens have a well characterized toxicity profile. Overall, AEs frequently seen with these regimens include fatigue, hematologic toxicity, gastrointestinal toxicity (nausea, vomiting, diarrhea), neurotoxicity, and hypersensitivity reactions. In order to minimize the occurrence of chemotherapy-related AEs, detailed dose modification guidelines to be followed in the event of chemotherapy-related toxicity are also provided.

Two studies in patients with advanced ovarian cancer are evaluating avelumab in combination with chemotherapy: Study B9991009 uses the combination of avelumab plus pegylated liposomal doxorubicin and Study B9991010 uses the combination of avelumab plus carboplatin/paclitaxel. While results by treatment arm from both studies are blinded to the Pfizer teams, early data have been reviewed by external data monitoring committees and both studies have been deemed safe to continue.

As mentioned above, combination of PD-1/ PD-L1 inhibitors with chemotherapy has resulted in increased clinical activity for the combination relative to chemotherapy alone. In addition, the safety profile of each combination does not significantly differ from the one of each agent alone. For example, in the KEYNOTE-021 study of carboplatin and pemetrexed with or

without pembrolizumab in patients with advanced non-squamous NSCLC, the frequency of ≥ Grade 3 AEs was 40% (23/59) in the chemotherapy plus pembrolizumab arm compared to 25% (16/62) in the chemotherapy alone arm. There was no increased risk of immune-mediated AEs in patients treated with chemotherapy plus pembrolizumab as compared to the known safety profile of single-agent pembrolizumab. Further, there was no increased risk of AEs leading to permanent discontinuation or to death in the chemotherapy plus pembrolizumab combination arm.

Overall, given the distinct mechanisms of action and toxicity profiles of avelumab and the selected chemotherapy regimens, relevant safety concerns are not expected from these combinations. The most frequently observed severe toxicities of avelumab are largely non-overlapping with the ones of the chemotherapy agents to be evaluated in the present study.

Since the chemotherapy agents are small molecules, there is no expectation of any drug-drug interaction between these agents and avelumab, as it is a mAb. To confirm, the PK of avelumab, the chemotherapy agents, and any other immunotherapies used in future portions of this study will be assessed in this study to evaluate the drug-drug interaction potential in an exploratory manner within each of the combinations.

For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

In this study, each of the selected chemotherapy doublets is dosed on a Q3W schedule. In an effort to mitigate unexpected hematologic toxicity and considering that the tolerability of avelumab in patients with severe myelosuppression is currently not well characterized, a Q3W schedule was adopted for avelumab in this study in order to avoid dosing of avelumab during the expected hematologic nadir period for the selected chemotherapy regimens.

As previously described, the 2 tumor types selected for evaluation in this study are sensitive not only to chemotherapy, but also to inhibitors of the PD-1/PD-L1 axis. Of particular importance to this study, avelumab has demonstrated antitumor activity in each tumor type. First-line treatment of patients with advanced non-squamous NSCLC with chemotherapy in combination with a PD-1 inhibitor, pembrolizumab, resulted in significantly improved median PFS and ORR compared to those seen with chemotherapy alone.[27] Based on clinical data for each agent alone and, as available, in combination with other agents to be used in this study, and considering data from combinations including similar drugs, the conduct of this trial with the initial combination of avelumab plus chemotherapy is considered justifiable. Given the different mechanisms of action of each of the agents to be used in this study, increases in the rate or severity of toxicities seen are not expected compared to when each agent is used independently. Thus, the projected benefit/risk of avelumab given in combination with chemotherapy is anticipated to be favorable for investigation in these populations of patients with advanced solid tumors. Any combination in this study shall be discontinued in the event of any new findings that indicate a significant deterioration of the risk-benefit relationship that would render continuation of the combination unjustifiable.

1.4. Biomarker Rationale

This study intends to characterize the ability of chemotherapy in isolation or together with various immunotherapies to increase the clinical benefit seen with single-agent avelumab. As the immunotherapies may vary with respect to targets engaged, target modulation needed for optimal activity and amount of prior clinical experience, some customization of the biomarker strategy will be needed for each combination tested. The following represents an overview of the planned strategy, followed by comments specific to each combination. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

The success of the combinations being tested will likely be contingent on identifying the specific tumor types and/or patients most likely to respond to the combination. Successful response to immunotherapy relies upon recognition of a tumor by the immune system, which is impacted by 3 factors:

1. The cell intrinsic immunogenicity of any tumor cells, for example their expression of MHC or of surface molecules such as PD-L1, which will determine whether tumor reactive immune cells can effectively recognize and kill the tumor cells.

2. The cell extrinsic immunogenicity of the tumor microenvironment, for example the presence or absence of suppressive cells such as Tregs or MDSCs, which will significantly impact the ability of tumor reactive immune cells to function.

3. The antigenicity of the tumor, that is how many mutations are present within the tumor, and whether those mutations generate recognizable T cell epitopes that might lead to priming of the immune response and subsequent targeting and elimination of the tumor.

The collection of pre-treatment tumor tissue, archival and/or *de novo* biopsy is mandatory for this study in order to enable assessments that inform as to these 3 factors. Parameters that may be studied include, but are not limited to, assessment of PD-L1 expression by tumor and/or immune cell types in the tumor using immunohistochemistry (IHC), CCI [redacted]

As noted above, chemotherapy has the potential to alter both the tumor cell intrinsic and extrinsic immunogenicity of the tumor, and an additional component of the biomarker plan for this study is to assess and confirm such changes within the tumor following treatment. To this end, collection of on-treatment tumor biopsies is mandatory unless clinically contraindicated in order to enable the parameters listed above to be compared pre- and post-treatment. These paired measurements are performed with the aim of identifying PD or mechanistic biomarkers for the combinations being tested, which could help inform optimal

dose and schedule for the combinations, aid in confirming activity for the combinations and, in the event that clinical benefit is not observed or is transient, may help inform as to the reasons for lack of benefit. A comparison will be made between paired biopsy data from patients receiving the 800 mg dose of avelumab and from patients receiving the 1200 mg avelumab dose in order to assess any quantitative or qualitative differences in the pharmacodynamic responses observed at different dose levels.

CCI

Biopsies at end of treatment in the event of discontinuation due to progressive disease are also requested from patients unless clinically contraindicated. Collection and analyses of these biopsies will enable exploration of the possible causes for lack of clinical benefit or for emerging resistance to therapy.

CCI

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

- Phase 1b lead-in: To assess DLT rate of avelumab in combination with chemotherapy, as first-line treatment in patients with locally advanced or metastatic solid tumors.

- To assess, per RECIST v1.1 (Appendix 3), the ORR of avelumab in combination with chemotherapy, as first-line treatment in patients with locally advanced or metastatic solid tumors.

Secondary Objectives

- To assess the overall safety and tolerability of avelumab in combination with chemotherapy;

- To characterize the PK of avelumab and chemotherapy when given in combination;

- To evaluate the immunogenicity of avelumab, when given in combination with chemotherapy;

- To assess the antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy;

- To assess the correlation of antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy, with mutational load in baseline tumor tissue;

- To assess the correlation of PD-L1 expression in baseline tissue and changes in this marker on-treatment, with antitumor activity, per RECIST v1.1, of avelumab in combination with chemotherapy.

CCI

2.2. Endpoints

Primary Endpoints

- Phase 1b lead-in: First 2 cycles DLT.
- Confirmed OR, as assessed by the Investigator using RECIST v1.1.

Secondary Endpoints

- AEs as characterized by type, severity (as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.4.03), timing, seriousness, and relationship to study treatments;
- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing;
- PK parameters of avelumab;
- PK parameters of chemotherapies, as data permit;
- ADA levels;
- Time-to-event endpoints including PFS, duration of response (DR), and time to tumor response (TTR), as assessed by the Investigator using RECIST v1.1; and OS;
- Mutational load within baseline tumor tissue;
- PD-L1 expression in baseline and on-treatment tumor tissue.

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b/2, open-label, multi-center, safety, clinical activity, PK, and PD study of avelumab in combination with chemotherapy with or without other anti-cancer immunotherapies, as first-line treatment of adult patients with locally advanced or metastatic solid tumors. Initially, avelumab will be evaluated in combination with standard-of-care chemotherapy in patients with advanced non-squamous NSCLC and cisplatin-eligible urothelial cancer (UC). These two tumor types were selected for study because they are responsive to chemotherapy, which currently is first-line standard-of-care for these indications. In addition, avelumab has shown preliminary evidence of clinical activity in both non-squamous NSCLC and UC.

Given the growing preclinical and clinical indications that combinations of anti-cancer immunotherapies potentially improve patient outcomes compared to results seen with single agents, in portions of the study to be added in the future, avelumab will be evaluated in combination with both standard-of-care chemotherapy and other anti-cancer immunotherapies in patients with advanced malignancies. Addition of new therapy combinations will be based on emerging preclinical and clinical data supportive of the tolerability and potential clinical benefit of each agent to be combined (eg, chemotherapy, anti-cancer immunotherapy agents) with avelumab and will be accomplished by protocol amendment. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

- Group A: avelumab plus chemotherapy alone:
    - Cohort A1: avelumab 800 mg Q3W plus pemetrexed/carboplatin in patients with non-squamous NSCLC;
    - Cohort A2: avelumab 800 mg Q3W plus gemcitabine/cisplatin in patients with cisplatin-eligible UC;
    - Cohort A3: avelumab 1200 mg Q3W plus pemetrexed/carboplatin in patients with non-squamous NSCLC;
    - Cohort A4: avelumab 1200 mg Q3W plus gemcitabine/cisplatin in patients with cisplatin-eligible UC.

Each combination cohort will be studied in 2 phases: 1) a Phase 1b lead-in to evaluate preliminary safety of the combination, and 2) a Phase 2 cohort expansion to evaluate preliminary efficacy and further evaluate safety. Phase 2 cohort expansion may be initiated only for the highest dose of avelumab deemed safe in each combination.

Phase 1b Lead-in

The safety of avelumab will be assessed independently in combination with each of the two different chemotherapy regimens.

The 1200 mg Q3W dosing regimen is being explored additionally in this Phase 1b/2 trial since it is projected to maintain the avelumab average exposures close to those observed with the approved dose of 10 mg/kg Q2W while extending the dosing interval for use in combination with Q3W chemotherapy regimens

Up to 12 patients will be enrolled into each cohort and evaluated for DLT (defined in Section 3.3) during the first 2 cycles of treatment as follows:

Cohorts A1 and A2:

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:
    - If ≤1 of 6 patients experience DLT in Cohort A1 (or A2), enrollment will be initiated in Phase 1b Cohort A3 (or A4);
    - If ≥3 of up to 6 patients experience DLT in Cohort A1 (or A2), enrollment in Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination;
    - If 2 of 6 patients experience DLT in Cohort A1 (or A2), the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b Cohort A1 (or A2);
        - If ≤3 of 12 patients experience DLT in Cohort A1 (or A2), enrollment may be initiated in Phase 1b Cohort A3 (or A4);
        - If ≥4 of up to 12 patients experience DLT in Cohort A1 (or A2), enrollment in the Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination.

Cohorts A3 and A4:

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:
    - If ≤1 of 6 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy; there will not be any enrollment in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;

- If ≥3 of up to 6 patients experience DLT in Cohort A3 (A4), enrollment in Cohort A3 (or A4) will be discontinued; enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;

- If 2 of 6 patients experience DLT in Cohort A3 (or A4), the Cohort A3 (or A4) will be expanded to enroll up to 6 additional DLT-evaluable patients;

    - If ≤3 of 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy; there will not be any enrollment in Phase 2 Cohort A1 (or A2) with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;

    - If ≥4 of up to 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy.

Phase 2 Cohort Expansion

If investigational products administration in the Phase 1b Lead-in portion of a given cohort is deemed safe based on the criteria described in "Phase 1b Lead-in" Section, then enrollment into that cohort may continue into the Phase 2 Cohort Expansion. The dose of avelumab to be administered in the Phase 2 Cohort Expansion (800 mg Q3W for Cohorts A1 and A2 or 1200 mg Q3W for Cohorts A3 and A4) will be determined based on the number of observed DLTs as described in "Phase 1b Lead-in" section. The highest dose level of avelumab deemed safe for the combination will be advanced.

For the cohort of patients with cisplatin-eligible UC selected to expand to Phase 2, up to approximately 40 patients, including those enrolled in Phase 1b Lead-in and those enrolled in the Phase 2 Cohort Expansion, will be treated with the combination of avelumab and chemotherapy with or without other immunotherapies. For the cohort of patients with non-squamous NSCLC selected to expand to Phase 2, approximately 20 patients, including those enrolled in Phase 1b Lead-in and those enrolled in the Phase 2 Cohort Expansion, will be treated with the combination of avelumab and chemotherapy with or without other immunotherapies. Up to approximately 80 patients in the Phase 1b lead-ins and Phase 2 cohort expansions combined for cisplatin-eligible UC and non-squamous NSCLC will be enrolled in Group A.

In future portions of the study, up to approximately 40 patients in each cohort (including those enrolled in Phase 1b lead-in and those enrolled in Phase 2) will be enrolled and treated with avelumab plus chemotherapy in the initial portion of the study and, in future portions of the study, with avelumab plus chemotherapy with or without other anti-cancer immunotherapies. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

For both Phase 1b lead-in and Phase 2 cohort expansion, all patients will initially receive either avelumab in combination with chemotherapy (Group A) or avelumab in combination with chemotherapy and other anti-cancer immunotherapies in portions of the study to be added in the future. Patients will continue to receive study treatment until disease progression is confirmed by the Investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. In Cohorts A1 and A3, treatment with carboplatin and pemetrexed will continue for a maximum of 4-6 cycles; in addition, maintenance therapy with pemetrexed may be administered at the discretion of the Investigator. In Cohorts A2 and A4, treatment with chemotherapy will continue until optimal response is achieved.

If discontinuation of chemotherapy is required for any reasons other than PD or protocol-specified limits, treatment with avelumab (Group A) or avelumab and/or the other anti-cancer immunotherapies in future portions of the study should be continued.

Patients who stop avelumab or the other anti-cancer immunotherapies for unacceptable toxicity may continue treatment with the investigational product(s) (eg, chemotherapy) that is/are not considered to be responsible for the toxicity observed.

3.1.1. Tumor Assessments

Antitumor activity will be assessed by radiological tumor assessments at 6-week intervals, using RECIST v1.1. In case PR or CR is observed according to RECIST v1.1, tumor assessment should be repeated at least 4 weeks after initial documentation. After 1 year from the first dose of study treatment, tumor assessments will be conducted at 12-week intervals until PD per RECIST v1.1. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration). Details of the treatment after initial evidence of radiological disease progression are provided in Section 5.4.5.

Further specific guidance on tumor imaging is provided in Section 7.6.

3.1.2. Safety Assessments

Safety will be monitored at regular intervals throughout the study by means of laboratory tests and clinical visits as reported in the Schedule of Activities and described in Section 7.1.

3.1.3. Pharmacokinetic/Immunogenicity Assessments

PK and immunogenicity blood sampling will be collected for each combination as described in the Schedule of Activities and Section 7.2.

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

3.1.4. Biomarker Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate biomarkers that are potentially predictive of treatment benefit with the combination of avelumab and chemotherapy with or without other immunotherapies. C
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[redacted] For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included. Biomarker assessments are described in Section 7.4.

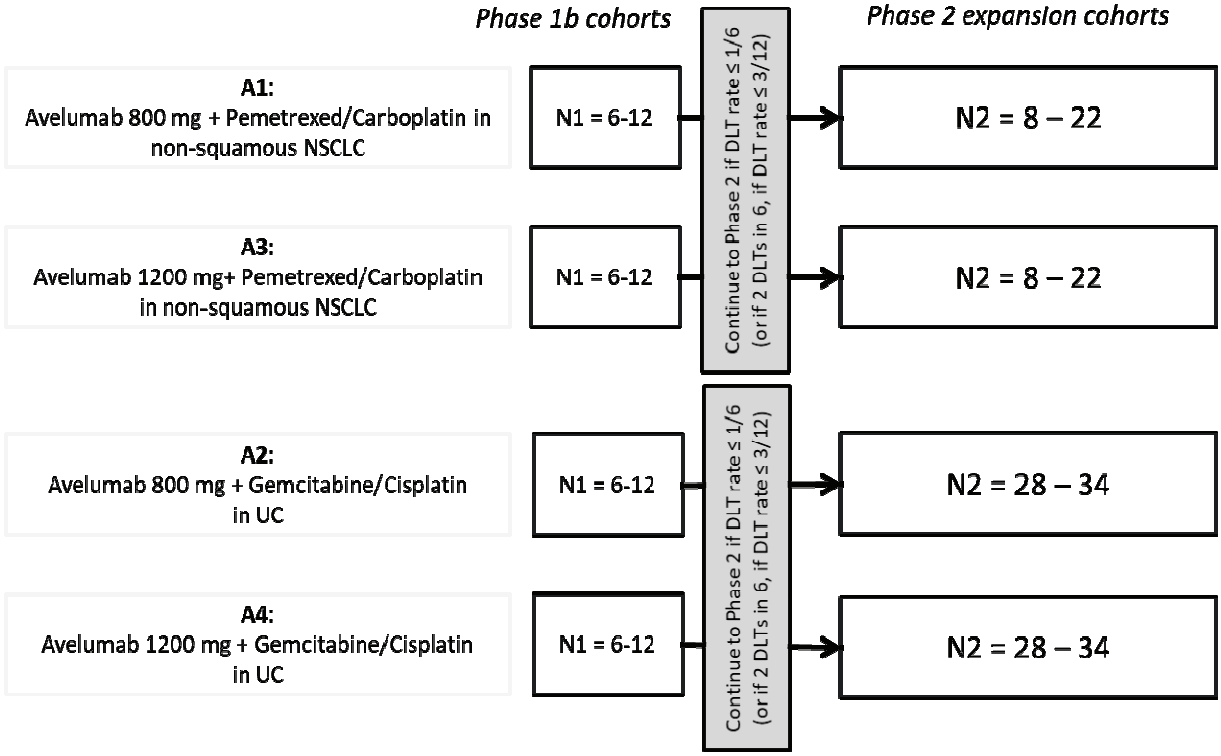
3.2. Study Designs for Each Group

Each combination will be administered in 21-day cycles. The DLT observation period for evaluation of each dose level during Phase 1b lead-in is the first 2 cycles of treatment.

3.2.1. Group A (Avelumab plus Chemotherapy)

Group A (Cohorts A1, A2, A3 and A4) will evaluate the combination of avelumab with chemotherapy in patients with non-squamous NSCLC or cisplatin-eligible UC. The study design is illustrated in Figure 1.

Figure 1. Group A (Avelumab plus Chemotherapy)



Refer to Section 3.1- Phase 1b Lead-in and Phase 2 Cohort Expansion.

3.3. Dose-Limiting Toxicity Definition

Severity of adverse events will be graded according to CTCAE version 4.03. Any of the following AEs occurring in the first 2 cycles (cycle duration with no delays is 21 days) of treatment during the Phase 1b lead-in of each cohort that are attributable to one or more of the investigational products will be classified as DLTs:

Hematologic:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/mm^3 or <0.5 x 10^9/L) lasting >7 days;
- Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (>101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour;
- Neutropenic infection (ANC <1,000/mm^3 or <1.0 x 10^9/L, and Grade >3 infection);
- Grade ≥3 thrombocytopenia (platelet count <50,000 - 25,000/mm^3 or <50.0 –25.0 × 10^9/L) with bleeding;
- Grade 4 thrombocytopenia (platelet count <25,000/mm^3 or <25.0 x 10^9/L);
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated).

Non-Hematologic:

- Grade 4 toxicities;
- Grade 3 toxicities persisting for >3 days despite adequate medical management (eg, nausea, vomiting, and diarrhea) except for endocrinopathies controlled with hormonal therapy;
- Potential Hy's law cases defined as: ALT or AST >3 x the upper limit of normal (ULN) if normal at baseline OR ALT or AST doubling the baseline (if > ULN at baseline) associated with total bilirubin >2 x ULN and an alkaline phosphatase <2 x ULN;
- In an asymptomatic patient, Grade 3 QTcF prolongation (QTcF ≥501) will first require repeat testing, re-evaluation by a qualified person, and correction of reversible causes, such as electrolyte abnormalities or hypoxia, for confirmation. If, after correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event should be considered a DLT.

Non-Adherence to Treatment Schedule:

- Delay of ≥3 weeks in receiving the next scheduled administration due to persisting treatment-related toxicities;

- Failure to deliver at least 75% of the planned doses of each of the investigational products during the first 2 cycles due to treatment-related toxicities.

Grade ≥3 laboratory abnormalities without a clinical correlate and not requiring medical intervention DO NOT constitute a DLT. Grade ≥3 laboratory abnormalities also have to represent a clinically relevant shift from baseline to be considered a DLT.

While the rules for adjudicating DLTs are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between Sponsor and Investigator, based on the emerging safety profile for the combinations.

During the Phase 1b lead-in, patients who did not receive at least 75% of the planned doses of investigational products during the first 2 treatment cycles for reasons other than investigational products-related toxicity are not evaluable for DLT. Additional patients will be enrolled in the specific cohort to replace those patients who are not considered DLT evaluable.

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.

Eligibility criteria specific to each unique combination of avelumab and chemotherapy with or without other immunotherapies are indicated.

4.1. Inclusion Criteria

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

1. Histological diagnosis of locally advanced (primary or recurrent) or metastatic solid tumor that is not amenable for treatment with curative intent as follows:

    - For all groups:

        - Measurable disease by RECIST v1.1 with at least 1 measurable lesion;

        - No prior systemic treatment for unresectable locally advanced or metastatic disease for the tumor type under study. If prior systemic chemotherapy treatment was given in the adjuvant or neo-adjuvant setting or as part of radiotherapy-chemotherapy treatment, disease free interval after stop of systemic treatment must be more than 6 months for non-squamous NSCLC and more than 12 months for UC;

- Availability of tumor specimens: A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block sufficient in size to allow for sectioning of at least 10 slides must be available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy. The archived sample must have been taken within 18 months prior to enrollment, with no intervening systemic anti-cancer therapy. If such an archived sample is not available, a de novo (ie, fresh) tumor sample must be obtained prior to enrollment. If blocks cannot be provided, then at least 10, but preferably 15, freshly prepared slides must be provided. Core needle or excision biopsies are required. If a patient has only one measurable (target) lesion and no suitable archived tumor tissue to serve as a baseline sample, then that one measurable (target) lesion should not be biopsied and that patient is not eligible for enrollment.

- For Group A:

  - Non-squamous NSCLC, with no activating EGFR mutations, ALK or ROS1 translocations/rearrangements. If monotherapy pembrolizumab is available as a standard of care treatment option, patients must have a tumor proportion score (TPS) <50% for PD-L1 (via the 22C3 pharmDx or the Ventana (SP263) PD-L1 IHC assay);

  - Transitional cell carcinoma of the urothelium including the bladder, urethra, renal pelvis, and ureter.

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

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

4. Estimated life expectancy of at least 90 days.

5. Adequate hepatic function defined by a total bilirubin level ≤1.5 × ULN, an AST level ≤2.5 × ULN, and an ALT level ≤2.5 × ULN.

6. Adequate renal function defined by an estimated creatinine clearance ≥50 mL/min according to the Cockcroft-Gault formula or by 24 hour urine collection for creatinine clearance or according to local institutional standard method.

7. Adequate bone marrow function including: ANC ≥1,500/mm^3 or ≥1.5 × $10^{9/}$L; platelets ≥100,000/mm^3 or ≥100 × 10^9/L; hemoglobin ≥9 g/dL (may have been transfused).

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

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

10. Pregnancy test (for females of childbearing potential) negative at screening. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

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

    c. Have medically confirmed ovarian failure.

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

4.2. Exclusion Criteria

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

1. Prior immunotherapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-OX-40, anti-glucocorticoid induced tumor necrosis factor (TNF) receptor (GITR), anti-lymphocyte activation gene-3 (LAG-3), anti-T cell immunoglobulin and mucin (TIM-3) domain, or anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibody (including ipilimumab), IDO1 inhibitor, or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways.

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 enrollment, have discontinued corticosteroid treatment for these metastases for at least 14 days, and are neurologically stable.

3. Diagnosis of any other malignancy within 2 years prior to enrollment. Adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the bladder, breast, or cervix, or low grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration) are allowed.

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

5. Active or prior 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.

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

7. Active infection requiring systemic therapy.

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

9. 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).

10. Vaccination within 4 weeks of the first dose of investigational product is prohibited except for administration of inactivated vaccines.

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

12. Known prior severe hypersensitivity to platinum-related compounds for all cohorts, to pemetrexed for patients enrolled in Cohorts A1 and A3, and to gemcitabine for patients enrolled in Cohorts A2 and A4 (NCI CTCAE v4.03 Grade ≥3).

13. Persisting toxicity related to prior therapy (NCI CTCAE v4.03 Grade >1); however alopecia, sensory neuropathy Grade ≤2, or other Grade ≤2 AEs not constituting a safety risk based on Investigator's judgment are acceptable.

14. Known history of colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis.

15. Ongoing cardiac dysrhythmias of NCI CTCAE v4.03 Grade ≥2 or prolongation of the QTcF interval to >480 msec.

16. 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.

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

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

19. Concurrent treatment with a prohibited medication listed in protocol Section 5.7.

20. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

21. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

22. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use at least 1 highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 90 days after the last dose of chemotherapy (for male and female patients) or at least 30 days after the last dose of avelumab (for female patients), whichever is longer.

4.3. Lifestyle Guidelines

In this study, fertile male patients and female patients who are of childbearing potential will receive chemotherapy, which has been associated with suspected or demonstrated teratogenicity/fetotoxicity. Patients will also receive avelumab and, in portions of the study to be added in the future, other anti-cancer immunotherapy, for which the teratogenic risk is not known. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included. Patients who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 method of highly effective (failure rate <1% per year) contraception, preferably with low user dependency, throughout the study and for at least 90 days after the last dose of chemotherapy (for male and female patients) or at least 30 days after the last dose of avelumab (for female patients), whichever is longer. The Investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected at least 1 highly effective method of contraception, preferably with low user dependency, for the individual patient and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the patient has been instructed in the consistent and correct use of this contraceptive method. At time points indicated in the Schedule of Activities, the Investigator or designee will inform the patient of the need to use at least 1 highly effective method of contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the Investigator or designee will instruct the patient to call immediately if the

selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner.

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

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the women of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal;
    - transdermal;
    - injectable.
- Progestogen-only hormone contraception associated with inhibition of ovulation:
    - oral;
    - injectable.
- Sexual abstinence:

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

All sexually active male patients must agree to prevent potential transfer of and exposure of partner(s) to chemotherapy through ejaculate by using a condom consistently and correctly, beginning with the first dose of study treatments and continuing for at least 90 days after the last dose of chemotherapy or longer as required by local regulations.

4.4. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). This is a study of avelumab in combination with chemotherapy with or without other immunotherapies. The investigational products to be evaluated in this study are described in Table 5.

Avelumab 800 mg (Cohorts A1 and A2) or 1200 mg (Cohorts A3 and A4) fixed dose will be administered as a 1-hour (hr) intravenous (IV) infusion on Day 1 of each 21-day cycle.

Each chemotherapy doublet will be administered IV as shown below per local guidelines.

Table 5. Investigational Products

Investigational Product	Dose(s) and Schedule (21-day cycle)[a,b]	Cohorts	Tumor Type
Avelumab[c]	800 mg or 1200 mg, Day 1 IV over 60 minutes	All	All
Pemetrexed/Carboplatin[c]		A1, A3	Non-squamous NSCLC
Pemetrexed	500 mg/m^2, Day 1 IV over 10 minutes		
Carboplatin	AUC 5, Day 1 IV over 60 minutes		
Gemcitabine/Cisplatin		A2, A4	UC
Gemcitabine	1000 mg/m^2, Day 1 and Day 8 IV over 30 minutes		
Cisplatin	70 mg/m^2, Day1 IV over 60 minutes		

AUC=area under the curve; IV=intravenously; NSCLC=non-small cell lung cancer; UC=urothelial cancer

[a] Order of administration for agents in each chemotherapy doublet is as appears in the table. For example, for the pemetrexed/carboplatin doublet, pemetrexed is administered prior to carboplatin.

[b] Durations of chemotherapy infusions shown are recommended. Sites are advised to follow their local guidelines.

[c] Avelumab dosed at 800 mg Q3W in Cohorts A1 and A2 and at 1200 mg Q3W in Cohorts A3 and A4.

5.1. Allocation to Treatment

Each combination will be evaluated in 2 study phases: a Phase 1b lead-in and a Phase 2 cohort expansion.

At the time that a patient has signed informed consent and entered screening, the site should contact the interactive response technology (IRT) system to obtain the patient identification number. Once a patient has met all eligibility criteria and has been assigned to the appropriate cohort by the Sponsor study team or designee, patient enrollment and allocation of investigational product will be managed by the IRT system. The site will need to contact the IRT system to enroll the patient and to obtain the study drug allocation information. Study treatment must be initiated preferably on the day of enrollment, but no later than 3 days after enrollment. See Schedule of Activities. At the time of enrollment, site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including, but not limited to, the user's identification (ID) and password, the protocol number, and the patient number. The IRT system will then provide a treatment assignment and dispensable unit (DU) or vial or bottle number for each investigational product to be dispensed. The IRT system will also provide a confirmation report containing the patient number and DU or vial or bottle numbers assigned. The confirmation report must be stored in the site's files.

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.

Enrollment into Cohort A1, A2, A3 and A4 will follow the sequential steps below:

- Enroll and assess safety of the A1 and A2 Phase 1b lead-in cohorts;
- Enroll and assess safety of the A3 and A4 Phase 1b lead-in cohorts;
- Enroll Phase 2 cohort expansions (A1 or A3 for non-squamous NSCLC; A2 or A4 for cisplatin-eligible UC) provided investigational products administration in a given cohort is deemed safe in Phase 1b-lead in according to the criteria described in Section 3.1.

Patients are not allowed to crossover between the different cohorts evaluated in this study.

5.2. Treatment Duration

For both Phase 1b lead-in and the Phase 2 cohort expansion, all patients will initially receive either avelumab in combination with chemotherapy (Group A) or avelumab in combination with chemotherapy and other anti-cancer immunotherapies in portions of the study to be added in the future. Patients will continue to receive study treatment until disease progression is confirmed by the Investigator, patient refusal, unacceptable toxicity, or until the study is terminated by the Sponsor, whichever occurs first. In Cohorts A1 and A3, treatment with carboplatin and pemetrexed will continue for a maximum of 4-6 cycles; in addition, maintenance therapy with pemetrexed may be administered at the discretion of the Investigator. In Cohorts A2 and A4, treatment with chemotherapy will continue until optimal response is achieved.

If discontinuation of chemotherapy is required for any reasons other than PD or protocol-specified limits, treatment with avelumab (Group A) and/or the other anti-cancer therapies in future portions of the study should be continued.

Patients who stop avelumab or the other anti-cancer immunotherapies in future portions of the study for unacceptable toxicity may continue treatment with the investigational product(s) (eg, chemotherapy) that is/are not considered to be responsible for the toxicity observed.

For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

5.3. Patient Compliance

5.3.1. Avelumab and Chemotherapy

For each administration of avelumab and chemotherapy, the site will complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent /required information on the preparation and administration of the dose.

This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

All doses of investigational products (avelumab and chemotherapy) will be by the appropriately designated study staff at the investigator site.

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

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

5.4. Investigational Product Supplies and Administration

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

5.4.1. Avelumab

Avelumab 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 products in accordance with the protocol and any applicable laws and regulations.

5.4.1.1. Dosage Form and Packaging

Avelumab is a sterile, clear, and colorless solution intended for IV administration. It is presented with a nominal volume of 10 mL at a concentration of 20 mg/mL in single-use glass vials closed with a rubber stopper and sealed with an aluminum polypropylene flip off seal. The vial is intended for single use only.

Packaging and labeling of avelumab 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 under refrigerated conditions (2°C to 8°C) that are monitored with temperature control monitoring devices.

5.4.1.2. Preparation

For avelumab, please see the Investigational Product (IP) Manual for instructions on how to prepare the investigational products for administration. The IV investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance, as well as trained in the procedures specified in this protocol.

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

Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration(s) for avelumab will be provided in the IP Manual.

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

5.4.1.3. Administration

Avelumab will be administered by IV infusion at the investigational site on an outpatient basis.

Avelumab will be administered as an 800 mg fixed dose via a 1-hour (-10/+20 minutes) IV infusion Q3W on Day 1 of each 3-week (21-day) cycle. Following each infusion of avelumab, patients must be observed for 30 minutes post-infusion for potential infusion related reactions. Patients should be instructed to report any delayed reactions to the Investigator immediately.

In order to mitigate avelumab infusion-related reactions, patients must be premedicated approximately 30 to 60 minutes prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Premedication will include an antihistamine (for example, 25-50 mg diphenhydramine IV or oral equivalent), and paracetamol (acetaminophen) (eg, 500-650 mg IV or oral equivalent). This regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids. On visits when both chemotherapy and avelumab are infused, avelumab will be infused after chemotherapy. If premedication for avelumab was administered prior to chemotherapy, the decision whether to repeat premedication prior to avelumab is at the discretion of the Investigator depending on the elapsed time and the half-life of corresponding premedication agent.

5.4.2. Chemotherapies

All chemotherapy agents (carboplatin, cisplatin, gemcitabine, and pemetrexed) will be supplied for the study by Pfizer Global Clinical Supply, Worldwide Research and Development. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 Code of Federal Regulations (CFR) 312.2(b) for Investigational New Drug (IND) exemption.

5.4.2.1. Dosage and Administration

For both the Phase 1b lead-in and Phase 2 cohort expansion, all patients will initially receive chemotherapy in combination with avelumab (Group A) or, in future portions of the study, chemotherapy in combination with avelumab and other anti-cancer immunotherapies until discontinuation of chemotherapy is required for any reason other than PD or protocol-specified limits. If discontinuation of chemotherapy is required for any reasons other than PD or protocol-specified limits, treatment with avelumab (Group A) or avelumab and/or the other anti-cancer immunotherapies in future portions of the study should be continued. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

For each chemotherapeutic agent, refer to the IP manual for preparation and administration instructions. Additional details for calculation of carboplatin dose based on the Calvert[40] formula can be found in Appendix 4.

For each chemotherapeutic agent, with the exception of pemetrexed, sites should follow local guidelines for specific pretreatments. For pemetrexed, the following premedications should be administered, as noted in the United States Prescribing Information, unless differently required by local guidelines:[41]

- Folic acid (400 – 1000 μg) orally once daily beginning 7 days prior to the first dose of pemetrexed and continuing daily through and including 21 days after the last dose of pemetrexed.
- Vitamin B12 (1 mg) intramuscularly beginning 1 week prior to the first dose of pemetrexed and every 3 cycles subsequently.
- Dexamethasone (4 mg) orally twice daily on the day before, the day of, and the day after each pemetrexed infusion.

All patients receiving chemotherapy should be weighed within 3 days of Day 1 prior to dosing for every cycle to ensure they did not experience either a weight loss or gain of >10% from the weight used for the last dose calculation. For weight change ≤10% the decision to recalculate the chemotherapy doses can be in accordance with institutional practice. 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 must be recalculated.

5.4.3. Timing of Investigational Product Administrations

In Group A, chemotherapy is administered prior to avelumab. The avelumab infusion is to be administered after the end of the infusion of the last chemotherapy agent.

For patients participating in the serial PK collection for chemotherapy on Cycle 2, chemotherapy and avelumab infusions are recommended to be performed as described in Table 2 and Table 4 on Cycle 2 Day 1, for ease of compliance with the protocol-defined PK blood and Electrocardiogram (ECG) collection times in relation to dosing of the three agents.

Premedications for chemotherapy agents should be administered as described in Section 5.4.2.1. When chemotherapy and avelumab are to be administered on the same day and premedication for avelumab was administered prior to chemotherapy, the decision whether to repeat premedication prior to avelumab infusion is at the discretion of the Investigator depending on the elapsed time and the half-life of corresponding premedication agent.

The infusion line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

The exact duration of each infusion should be recorded in both source documents and case report forms (CRFs). Dose reduction for toxicity management for avelumab is not permitted; however, next cycle administration of avelumab may be omitted or delayed due to persisting toxicity as described in Table 7 and Section 5.4.4.4.

On days when PK samples are taken, samples for each respective agent will be taken at the time relative to dosing of that specific agent as described in the Schedule of Activities tables.

5.4.4. Recommended Dose Modifications

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

In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom. In addition to dose modifications, Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Treatment/Dose modifications may occur independently for each drug in the combination based on the observed toxicity and the guidance provided below. All dose modifications must be clearly documented in the patient's notes and in the CRF.

Dose reductions are only allowed for chemotherapy (carboplatin, cisplatin, gemcitabine, and pemetrexed). No dose reductions are allowed for avelumab. Intra-patient dose escalation is not allowed for any of the study drugs at any time.

In the event that it becomes necessary to stop dosing with one or both of the two chemotherapeutic drugs in the combination, the patient should remain in the study and avelumab (Group A) may be continued uninterrupted at the Investigator's discretion.

In the event that it is necessary to permanently discontinue treatment with avelumab (Group A), the patient may continue to receive chemotherapy at Investigator's discretion.

5.4.4.1. Guidelines for Chemotherapy Toxicity Management

Dose modification (dose delays and dose reductions) for chemotherapy (carboplatin, cisplatin, gemcitabine, and pemetrexed) due to adverse drug reactions should be made in accordance with the guidance provided below, product labeling, and institutional guidelines.

Starting doses for each chemotherapeutic agent and dose reduction levels are described in Table 6.

For any adverse event of NCI CTCAE v4.03 Grade 3 and Grade 4 severity not covered in the following sections and considered at least possibly related to chemotherapy, treatment should be withheld until recovery to Grade ≤1 and then, at Investigator's discretion, the chemotherapy treatment should be permanently discontinued or dose should be reduced by one dose level as described in Table 6. If more than 2 dose reductions for one chemotherapy agent are necessary, the patient should discontinue from that chemotherapy agent. Treatment with avelumab (Group A) should be discontinued according to Section 5.4.4.4.

5.4.4.2. Dose Delays: All Investigational Products

Retreatment may not occur until all of the following parameters have been met:

- ANC is ≥1.0 x 10^9/L;
- Platelet count is ≥75 x 10^9/L (when gemcitabine or cisplatin is used the platelet count is ≥100 x 10^9/L);
- Calculated creatinine clearance as determined prior to each administration of study drug is at least ≥50 mL/min according to institutional standard practices (when pemetrexed or cisplatin are included in the chemotherapy regimen). For patients receiving cisplatin, if calculated creatinine clearance is ≥40 and <50 mL/min, treatment with cisplatin may continue, but cisplatin dose must be reduced by 50% from previous dose. For a given patient, the same method of creatinine clearance calculation should be used at each assessment.

All study drugs (including avelumab) will be delayed until the above criteria are met.

5.4.4.3. Dose Reductions: Chemotherapy

For chemotherapy (carboplatin, cisplatin, gemcitabine, or pemetrexed) the dose may need to be reduced when treatment is resumed based on the worst toxicity experienced in the previous cycle. Dose reductions may be independent for each drug in the combination based on the toxicity and the specific drug management recommendations. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intra-patient dose escalation is not allowed for any of the study drugs at any time. Dose reduction criteria are described below (Table 6) for each chemotherapy drug administered in this study.

Table 6. Dose Modification Levels for Chemotherapy (Cisplatin, Carboplatin, Pemetrexed, and Gemcitabine)

Drug	Starting Dose	Dose Level -1	Dose Level -2
		Reduce to 75% of starting dose.	Reduce to 50% of starting dose.
Gemcitabine	1000 mg/m^2		
Pemetrexed	500 mg/m^2		
Carboplatin	AUC 5		
Cisplatin	70 mg/m^2		

5.4.4.4. Dose Modifications for Avelumab

For avelumab, no dose reductions are permitted in this study, but the next avelumab infusion may be omitted or delayed based on persisting toxicity.

Recommended treatment modifications for avelumab due to drug-related toxicity are shown in Table 7.

Table 7. Avelumab Treatment Modifications for Drug-Related Toxicity

	NCI CTCAE Severity Grade	Avelumab Treatment Modification
Infusion-related Reaction / Hypersensitivity	Grade 1-4	See Section 5.4.4.5 and Table 8.
Immune-related AE (irAE)	Grade 1-4	See Section 5.4.4.6 and Table 9.
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. • Re-initiate once toxicity is Grade ≤1 or baseline. • Permanently discontinue if toxicities do not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (consider consult with the medical monitor before permanently discontinuing the treatment). **Exceptions are:** • Laboratory values that do not have any clinical correlate.
	Grade 4	• Permanently discontinue avelumab. **Exceptions are:** • Laboratory values that do not have any clinical correlate.

Avelumab infusion-related reactions, hypersensitivity reactions (Grades 1 to 4) and irAEs should be handled according to guidelines in Section 5.4.4.5 and Section 5.4.4.6.

5.4.4.5. Avelumab: Infusion-Related Reactions/Hypersensitivity Reactions

5.4.4.5.1. Special Precautions for Avelumab Administration

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

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

On visits when both chemotherapy and avelumab are infused, avelumab will be infused after chemotherapy. If premedication for avelumab was administered prior to chemotherapy, the decision whether to repeat pre medication prior to avelumab is at the discretion of the Investigator depending on the elapsed time and the half-life of corresponding premedication agent.

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

Following the infusions of avelumab, patients must be observed for 30 minutes post- infusion for potential IRRs. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms of avelumab IRRs include but are not limited to fever, chills, flushing, hypotension, dyspnea wheezing, back pain, abdominal pain, and urticaria. Management of avelumab infusion reactions is described in Table 8.

Table 8. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modifications
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the investigational product 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 infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the patient. • Patients must be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

* If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions.
IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Event, NSAIDs=nonsteroidal anti-inflammatory drugs.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 8 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed. 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.

5.4.4.6. Avelumab: Immune-Related Adverse Events Toxicity Management

Treatment of irAEs is mainly dependent upon severity (NCI CTCAE grade v4.03):

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

For patients receiving avelumab, any AE suspected to be immune-related (irAE) should be managed according to the guidance for management of irAEs (Table 9). For Grade ≥3 suspected immune-related toxicities, chemotherapy may also be placed on hold until the irAE resolved to Grade 1, based on the Investigator's medical judgment.

Table 9. Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Grade of Diarrhea/Colitis (NCI CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: <4 stools/day over baseline; Colitis: asymptomatic	• Continue avelumab therapy • Symptomatic treatment (eg, loperamide)	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately • If worsens: • Treat as Grade 2, 3, or 4

Grade 2
Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL
Colitis: abdominal pain; blood in 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 to 4

Grade 3 to 4
Diarrhea (Grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL
Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs
Grade 4: life-threatening, perforation
	• Withhold avelumab for Grade 3
	• Permanently discontinue avelumab for Grade 4 or recurrent Grade 3
	• 1.0 to 2.0 mg/kg/day IV prednisone or equivalent
	• Add prophylactic antibiotics for opportunistic infections
	• Consider lower endoscopy
		• If improves:
		  • Continue steroids until Grade 1, then taper over at least 1 month; resume avelumab following steroids taper (for initial Grade 3)
		• If worsens, persists >3 to 5 days, or recurs after improvement:
		  • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Table 9. Management of 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 (eg, antihistamines, topical steroids)
		• If Grade 2 persists >1 to 2 weeks or recurs:
		  • Withhold avelumab therapy
		  • Consider skin biopsy
		  • Consider 0.5 to 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 of avelumab therapy • Monitor for symptoms every 2 to 3 days • Consider Pulmonary and Infectious Disease consults	• Re-assess at least every 3 weeks • If worsens: • Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	• Withhold avelumab therapy • Pulmonary and Infectious Disease consults • Monitor symptoms daily, consider hospitalization • 1.0 to 2.0 mg/kg/day	• Re-assess every 1 to 3 days • If improves: • When symptoms return to ≤ Grade 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper

Table 9. Management of Immune-Related Adverse Events

	prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	• 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 Grade ≤1:
		  • Taper steroids over at least 1 month
		• If not improving after 48 hours or worsening:
		  • Add additional immunosuppression (eg, infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Function Tests (LFT) 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 elevations persist >5 to 7 days or worsen:
		  • Treat as Grade 3 or Grade 4

Grade 3 to 4
AST or ALT >5 x ULN and /or total bilirubin >3 x ULN
	• Permanently discontinue avelumab therapy
	• Increase frequency of monitoring to every 1 to 2 days
	• 1.0 to 2.0 mg/kg/day prednisone or equivalent
	• Add prophylactic antibiotics for opportunistic infections
	• Consult gastroenterologist/ hepatologist
	• Consider obtaining MRI/CT scan of liver and liver biopsy
		• If returns to Grade ≤1:
		  • Taper steroids over at least 1 month
		• If does not improve in >3 to 5 days, worsens or rebounds:
		  • Add mycophenolate mofetil 1 gram (g) twice daily
		  • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

Table 9. Management of Immune-Related Adverse Events

	if clinically warranted	
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN–1.5 x ULN	• Continue avelumab therapy	• Continue renal function monitoring • If worsens: • Treat as Grade 2 to 3 or 4

Grade 2 to 3
Creatinine increased >1.5 and ≤6 x ULN
	• Withhold avelumab therapy
	• Increase frequency of monitoring to every 3 days
	• 1.0 to 2.0 mg/kg/day prednisone or equivalent
	• Add prophylactic antibiotics for opportunistic infections
	• Consider renal biopsy
		• If returns to Grade ≤1:
		  • Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
		• If worsens:
		  • Treat as Grade 4

Grade 4 Creatinine increased >6 x ULN	• Permanently discontinue avelumab therapy • Monitor creatinine daily • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy • Nephrology consult	• If returns to ≤Grade 1: • Taper steroids over at least 1 month
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and/or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	• Withhold avelumab therapy • Hospitalize • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management • Cardiology consult to establish etiology and rule-out immune-mediated myocarditis • Guideline based supportive treatment as per cardiology consult*	• If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy • If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis

Table 9. Management of Immune-Related Adverse Events

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

Table 9. Management of Immune-Related Adverse Events

	appropriate • Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis)	

Hypopituitarism/Hypophysitis (secondary endocrinopathies)	• If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH):
	  • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women)
	  • Hormone replacement/ suppressive therapy as appropriate
	  • Perform pituitary MRI and visual field examination as indicated
	• If hypophysitis confirmed:
	  • Continue avelumab if mild or moderate 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 prednisolone or equivalent) followed by corticosteroids taper during at least 1 month
	  • Add prophylactic antibiotics for opportunistic infections
		• Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement)
		• In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented
		• Continue hormone replacement/suppression therapy as appropriate

Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**

Table 9. Management of Immune-Related Adverse Events

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 resuming avelumab therapy • If irAE is confirmed, treated 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 investigational products therapy following steroids taper
Recurrence of same Grade 3 irAE	• 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 immunosuppressants as needed • Add prophylactic antibiotics for opportunistic infections • Specialty consult	• If improves to Grade ≤1: • Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	• Permanently discontinue avelumab therapy • Specialty consult	

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

5.4.4.7. Recommended Treatment Modifications for Pemetrexed, Carboplatin, Avelumab (Cohorts A1 and A3)

5.4.4.7.1. Hematological Toxicities

In the event of hematologic toxicities, treatment may be delayed to allow sufficient time for recovery, as described above. If patients develop hematologic toxicities Grade ≥3, therapy should be withheld until ANC is ≥1.0 x 10^9/L and platelet count is ≥75 x 10^9/L, or values returned to baseline levels. Upon recovery, dose adjustments for the chemotherapy at the start of a subsequent cycle should be based on nadir hematologic counts from the preceding cycle of therapy. Dose modification (dose delays and dose change) for pemetrexed and carboplatin due to adverse drug reactions should be made in accordance with the guidance provided below (Table 10), product labeling, and institutional guidelines.

Table 10. Pemetrexed, Carboplatin, Avelumab (Cohorts A1 and A3) Hematologic Toxicity Management

Hematologic Toxicity	Pemetrexed	Carboplatin	Avelumab
Grade 1 and Grade 2	Continue at the same dose level.	Continue at the same dose level.	Continue as per schedule
Grade 3 and 4	Delay dosing until • ANC ≥1.0 x 10^9/L and • platelets ≥75 x 10^9/L. Once blood counts have improved, pemetrexed can be reinitiated at the same dose level: Exception are: • Platelet Grade ≥3: Reduce to 75% of previous dose • Platelet Grade ≥3 with bleeding: Reduce to 50% of previous dose • ANC Grade 4: Reduce to 75% of previous dose.	Delay dosing until • ANC ≥1.0 x 10^9/L and • platelets ≥75 x 10^9/L. Once blood counts have improved, carboplatin can be reinitiated at the same dose level: Exception are: • Platelet Grade ≥3: Reduce to 75% of previous dose. • ANC Grade 4: Reduce to 75% of previous dose.	Delay dosing until • ANC ≥1.0 x 10^9/L and • platelets ≥75 x 10^9/L. then resume avelumab at the same dose level.

Note: hematological growth factors for neutropenia or anemia are allowed

5.4.4.7.2. Non-Hematological Toxicities

In the event of non-hematologic toxicities, treatment may be delayed to allow sufficient time for recovery. If patients develop non-hematologic toxicities Grade ≥3 (excluding neurotoxicity), therapy should be withheld until toxicity is Grade ≤1 or baseline. Upon recovery, dose adjustments at the start of a subsequent cycle should be based on the maximum non-hematologic toxicity from the preceding cycle of therapy. Dose modification (dose delays and dose change) for pemetrexed and carboplatin due to adverse drug reactions should be made in accordance with the guidance provided below (Table 11), product labeling and institutional guidelines.

For patients receiving avelumab, any adverse event suspected to be immune-related (irAE) should be managed according to the guidance for management of irAEs (Section 5.4.4.6, Table 9). For Grade ≥3 suspected immune-related toxicities or events requiring systemic corticosteroids/immunosuppressant, chemotherapy may also be placed on hold until the irAE resolved to Grade 1, based on Investigator's medical judgment.

Guidelines for the management of avelumab infusion-related reactions and hypersensitivity reaction are outlined in Section 5.4.4.5 and Table 8.

If there is a hypersensitivity reaction to carboplatin or pemetrexed, then this should be managed as per local institutional protocols. In the case of recurrent hypersensitivity reactions, despite adequate premedication, the drug (carboplatin or pemetrexed) may be discontinued at the discretion of the treating physician, and the patient may continue on treatment with single chemotherapeutic agent (either carboplatin or pemetrexed) in combination with avelumab.

Table 11. Pemetrexed, Carboplatin, Avelumab (Cohorts A1 and A3) Non-Hematologic Toxicity Management

Toxicity	Pemetrexed	Carboplatin	Avelumab
Adverse events with potential immune-related etiology (see Section 5.4.4.6)	Continue for Grade 1/2 events Pemetrexed may be placed on hold for events Grade ≥3 or events requiring corticosteroids / immunosuppressant, until the event resolves to Grade ≤1 based on Investigator's medical judgment and after discussion with the Sponsor	Continue for Grade 1/2 events Carboplatin may be placed on hold for events Grade ≥3 or events requiring corticosteroids / immunosuppressant, until the event resolves to Grade ≤1 based on Investigator's medical judgment and after discussion with the Sponsor	See Section 5.4.4.6 and Table 9
Neurotoxicity	Grade 1/2: continue at the same dose. Grade ≥3: permanently discontinue	Grade 1: continue at the same dose Grade 2: reduce to 50% Grade 3/4: permanently discontinue	See Section 5.4.4.4 and Table 7
Mucositis	Grade 1/2: continue at the same dose Grade ≥3: delay until recovery to Grade ≤1 and then resume at 50% of previous dose	Grade 1/2: continue at the same dose Grade ≥3: delay until recovery to Grade ≤1 and then resume at the same dose	See Section 5.4.4.4 and Table 7
Diarrhea	Grade 1/2: continue at the same dose Grade ≥3 or any grade requiring hospitalization: delay until recovery to Grade ≤1 and then resume at 75% of previous dose	Grade 1/2: continue at the same dose Grade ≥3: delay until recovery to Grade ≤1 and then resume at 75% of previous dose	See Section 5.4.4.6 and Table 9
IRR and Hypersensitivity	See Section 5.4.4.7.2.	See Section 5.4.4.7.2.	See Section 5.4.4.5 and Table 8

Toxicity	Pemetrexed	Carboplatin	Avelumab
Other Non-hematologic Toxicity	Grade 1/2: continue at the same dose Grade ≥3: at Investigator discretion's delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue **Exceptions are:** Laboratory values that do not have any clinical correlate.	Grade 1/2: continue at the same dose Grade ≥3: at Investigator discretion's delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue **Exceptions are:** Laboratory values that do not have any clinical correlate.	See Section 5.4.4.4 and Table 7

5.4.4.8. Recommended Treatment Modifications for Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4)

5.4.4.8.1. Hematologic Toxicities

In the event of hematologic toxicities, treatment may be delayed to allow sufficient time for recovery, as described above. If patients develop hematologic toxicities Grade ≥3, therapy should be withheld until ANC is ≥1.0 x 10^9/L and platelet count is ≥100 x 10^9/L for cisplatin dosing, or values returned to baseline levels. Upon recovery, dose adjustments at the subsequent dose should be based on nadir hematologic counts from the preceding dose of therapy. Dose modification (dose delays and dose change) for cisplatin and gemcitabine due to adverse drug reactions should be made in accordance with the guidance provided below (Table 12), product labeling and institutional guidelines.

Table 12. Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Hematologic Toxicity Management

Hematologic Toxicity	Cisplatin	Gemcitabine	Avelumab
Grade 1 and Grade 2	Continue at the same dose level. Exception is: • Platelets <100 x 10^9/L: delay dosing until platelets ≥100 x 10^9/L and then resume cisplatin at 75% of the previous dose	Continue at the same dose. Exception is: • Platelet <100 x 10^9/L: delay dosing until platelets ≥100 x 10^9/L and then resume gemcitabine at 75% of the previous dose.	Continue as per schedule
Grade 3 and 4	Delay dosing until • ANC ≥1.0 x 10^9/L and • platelets ≥100 x 10^9/L. Once blood counts have improved, cisplatin can be reinitiated at 75% of the previous dose level	Delay dosing until • ANC ≥1.0 x 10^9/L and • platelets ≥100 x 10^9/L. Once blood counts have improved, gemcitabine can be reinitiated at the same dose level.	Delay until • ANC is ≥1.0 x 10^9/L and • Platelet count is ≥75 x 10^9/L Then resume avelumab at the same dose level.

Note: hematological growth factors for neutropenia or anemia are allowed.

5.4.4.8.2. Non-Hematologic Toxicities

In the event of non-hematologic toxicities, treatment may be delayed to allow sufficient time for recovery, as described above. If patients develop non-hematologic toxicities Grade ≥3 therapy should be withheld until toxicity is Grade ≤1 or baseline. Upon recovery, dose adjustments at the subsequent dose should be based on the maximum non-hematologic toxicity from the preceding dose of therapy. Dose modification (dose delays and dose change) for cisplatin and gemcitabine due to adverse drug reactions should be made in accordance with the guidance provided below (Table 13), product labeling and institutional guidelines.

For patients receiving avelumab, any adverse event suspected to be immune-related (irAE) should be managed according to the guidance for management of irAEs (Section 5.4.4.6, Table 9). For Grade ≥3 suspected immune-related toxicities or events requiring corticosteroids/immunosuppressant, chemotherapy may also be placed on hold until the irAE resolved to Grade 1, based on Investigator's medical judgment.

Guidelines for the management of avelumab infusion-related reactions and hypersensitivity reaction are outlined in Section 5.4.4.5 and in Table 8.

If there is a hypersensitivity reaction to cisplatin or gemcitabine, then this should be managed as per local institutional protocols. In the case of recurrent hypersensitivity reactions, despite adequate premedication, the drug (cisplatin or gemcitabine) may be discontinued at the discretion of the treating physician, and the patient may continue on treatment with single chemotherapeutic agent (either cisplatin or gemcitabine) in combination with avelumab.

Table 13. Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Non-Hematologic Toxicity Management

Toxicity	Cisplatin	Gemcitabine	Avelumab
Adverse events with potential immune-related etiology (see Section 5.4.4.6)	Continue for Grade 1/2 events Cisplatin may be placed on hold for events Grade ≥3 or events requiring corticosteroids / immunosuppressant, until the event resolves to Grade ≤1 based on Investigator's medical judgment and after discussion with the Sponsor	Continue for Grade 1/2 events Gemcitabine may be placed on hold for events Grade ≥3 or events requiring corticosteroids / immunosuppressant, until the event resolves to Grade ≤1 based on Investigator's medical judgment and after discussion with the Sponsor	See Section 5.4.4.6. and Table 9
Neurotoxicity	Peripheral neurotoxicity • Grade 2: reduce to 75% of the previous dose • Grade ≥3: delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue Ototoxicity[a] • Grade 2 clinical hearing loss: reduce to 75% of previous dose. • Grade ≥3: delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue	No dose reductions are needed. Dose reduction may be reduced at Investigator's discretion.	See Section 5.4.4.4 and Table 7

Table 13 Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Non-Hematologic Toxicity Management (continued)

Toxicity	Cisplatin	Gemcitabine	Avelumab
Gastrointestinal toxicity (nausea or vomiting)	Grade 3 nausea or vomiting despite optimal antiemetic prophylaxis and therapy: delay until recovery to Grade ≤1 and then resume at same dose or at 75% of the previous dose Grade 4 vomiting despite optimal antiemetic prophylaxis and therapy: delay until recovery to Grade ≤1 and then resume at 50% of the previous dose	Grade ≥3 nausea or vomiting despite optimal antiemetic prophylaxis and therapy: delay until recovery to Grade ≤1 and then resume at same dose or at 75% of the previous dose	See Section 5.4.4.4 and Table 7
Hepatotoxicity	Grade 3: delay until recovery to Grade ≤1 and then resume at 75% of the previous dose Grade 4: delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue	Grade ≥3: permanently discontinue	See Section 5.4.4.6 and Table 9
IRR and Hypersensitivity	See Section 5.4.4.8.2.	See Section 5.4.4.8.2	See Section 5.4.4.5 and Table 8
Unexplained dyspnea or other evidence of severe pulmonary toxicity	Grade ≥3: delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue	Permanently discontinue	See Section 5.4.4.6 and Table 9
Renal toxicities	Serum creatinine >1.5 mg/dL AND creatinine clearance <40 mL/min, delay until: • Serum creatinine is <1.5 mg/dL OR • Creatinine clearance is ≥50 mL/min and Then resume at 50% of the previous dose Serum creatinine >1.5 mg/dL AND creatinine clearance ≥40 mL/min to <50 mL/min, continue dosing but reduce dose to 50% of previous dose	Grade ≥3: delay until recovery to Grade ≤1 and then resume at same dose or at 75% of the previous dose	See Section 5.4.4.6. and Table 9

Table 13 Cisplatin, Gemcitabine, Avelumab (Cohorts A2 and A4) Non-Hematologic Toxicity Management (continued)

Toxicity	Cisplatin	Gemcitabine	Avelumab
Other Non- hematologic Toxicity	Grade 1/2: continue at the same dose Grade ≥3: at Investigator's discretion delay until recovery to Grade ≤1 and then resume at 75% of the previous dose or permanently discontinue **Exceptions are:** Laboratory values that do not have any clinical correlate.	Grade 1/2: continue at the same dose Permanently Discontinue in case of: • Hemolytic-uremic syndrome • Capillary leak syndrome • Posterior reversible encephalopathy syndrome For other toxicity: • Grade ≥3: at Investigator's discretion delay until recovery to Grade ≤1 and then resume at 50% of the previous dose or permanently discontinue **Exceptions are:** Laboratory values that do not have any clinical correlate.	See Section 5.4.4.4 and Table 7

[a] Audiograms should be performed before starting treatment with cisplatin and then repeated as per local practice.

5.4.5. Treatment after Initial Evidence of Radiological Disease Progression

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

If radiologic imaging shows disease progression, patients may continue to receive avelumab (Group A) or, in portions of the study to be added in the future, avelumab plus other anti-cancer immunotherapies until the next scheduled tumor assessment if they are clinically stable. If chemotherapy dosing was ongoing at the time of PD determination, chemotherapy dosing should be discontinued until results of the next scheduled tumor assessment are available. Patients must meet the following criteria in order to be classified as clinically stable:

- 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.

For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

Patients who are deemed clinically unstable should be withdrawn from study treatment and should enter the follow-up portion of the study.

If repeat imaging no longer shows PD but rather CR, PR or SD compared to the baseline scan, treatment with avelumab may be continued in Group A or with avelumab and other anti-cancer immunotherapies in future versions of the study. In addition, treatment with chemotherapy may be resumed if the patient was receiving chemotherapy at the time of the initial determination of PD.

If the repeat imaging confirms PD, patients should be considered for discontinuation from all investigational products. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the investigational products. The Investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events, and laboratory data.

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

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

Patients who stop treatment for reasons other than toxicity with any of the investigational products and then experience radiologic disease progression shortly thereafter will be eligible for re-treatment with the investigational products they were receiving at the time of treatment discontinuation at the discretion of the Investigator and after discussion with the Sponsor.

5.4.6. Food Requirements

The IV investigational products (avelumab, chemotherapies) may be administered without regard to food.

5.5. Investigational Product Storage

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

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

For all investigational products, the storage conditions stated in the product's SRSD (eg, IB) for avelumab or local guidelines for all chemotherapy agents will be superseded by the storage conditions stated in the labeling.

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

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

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

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

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of all investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Medications

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 discretion of the treating physician.

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. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). Concomitant medications should be reviewed at each study visit, and any prohibited treatments (as described in Section 5.7) should be discussed with the patient and appropriately managed. Given that recording of non-serious AEs ends when a patient begins a new anti-cancer therapy (Section 8.1.4.2 Recording Non-serious AEs and SAEs on the CRF), recording of concomitant medications associated with these non-serious AEs should also end. Reporting of concomitant medications associated with SAEs should continue to be reported for up to 90 days after the last dose of study drug (Section 8.1.4.2), even if the patient begins a new anti-cancer therapy.

Concurrent anti-cancer therapy with agents other than study treatments is not allowed. Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

Recommended medications to treat infusion-related reactions and hypersensitivity reactions and immune-related events are reported in Section 5.4.4.5, and Section 5.4.4.6, respectively.

5.7.1. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the DLT observation period (eg, the first two cycles of treatment), but they may be used to treat emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines[44] or as allowed per local guidance.

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.7.2. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. In case of a surgical procedure, investigational products should be delayed. Postoperatively, the decision to reinitiate investigational products should be discussed with the Sponsor.

5.7.3. Concomitant Radiotherapy

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

5.7.4. Other Prohibited Concomitant Medicines and Therapies

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

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than investigational products.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.7.3).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Table 9). See below Clarification Regarding Steroid Use.

- Other experimental pharmaceutical products.

- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactivated vaccines (eg, influenza vaccine).

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

Clarifications Regarding Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[45,46] Furthermore, as with all immunotherapies intended to augment T-cell-mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit. However, studies with anti-CTLA-4 compounds indicate that short term use of steroids can be employed without compromising clinical outcomes.[47] Therefore, the use of steroids during this trial is restricted as follows:

- Premedication: steroid inclusion in the premedication regimen for chemotherapy as required per product label or local guidelines is allowed in all study arms.

- Therapeutic use: for the treatment of infusion-related reactions and for the treatment of irAEs, steroids are permitted according to the modalities indicated in Table 9.

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

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

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

5.8. Rescue Medications and Supportive Care

5.8.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

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

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice, assuming there is no expected drug-drug interaction with study treatments (see Section 5.7.4). Prophylactic administration should be considered for the cases outlined in Table 9.

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

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

6. STUDY PROCEDURES

6.1. Screening

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

6.1.1. Tumor Biospecimens

A mandatory archived FFPE tumor tissue block sufficient in size to allow for sectioning of at least 10 slides must be available from the most recent primary or metastatic tumor biopsy or resection prior to start of study therapy. The archived sample must have been taken within 18 months prior to enrollment, with no intervening systemic anti-cancer therapy. If such an archived sample is not available, a *de novo* (ie, fresh) tumor sample must be obtained prior to enrollment. The lesion to be biopsied must not be the only measurable (the only target) lesion.

FFPE tissue blocks should be provided if available and permitted by local laws and policies. If blocks cannot be provided for these reasons, then sections must be freshly cut (ie, cut no more than 30 days prior to shipment to the central laboratory), 5 µm thick and mounted on positively-charged microscope slides (SuperFrost Plus glass slides are recommended). A minimum of 10, but preferably 15, slides should be provided.

Subject to the availability of a biopsiable lesion that is not the only target lesion, collection of a biopsy on Cycle 2 Day 8 (-7 days to +2 days) (prior to dosing) and then as clinically indicated during treatment is mandatory unless clinically contraindicated. These on-treatment biopsies are required except in instances where the procedure poses unacceptable risks per Investigator documentation.

An optional biopsy at End of Treatment, if a patient discontinues due to disease progression, is requested except in instances where the procedure poses unacceptable risks per Investigator documentation. The tumor sample collected at the End of Treatment should be performed before initiation of subsequent anti-cancer therapy, preferably no later than 7 days after the End of Treatment visit.

See Schedule of Activities for timing of biopsies.

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

Guidance for Selection of Biopsy Site: If there are multiple measurable lesions that could serve as target lesions, one of these lesions may be the lesion that is biopsied. The biopsied lesion must not be assessed as a target lesion and must be distinct from the target lesions being followed for measurable disease. Most importantly, the biopsied lesion must be one that can be accessed safely. Biopsies from bone lesions should not be submitted.

If a patient has only one measurable lesion and, hence, only one target lesion and no suitable archived tumor tissue to serve as a baseline sample, then that one measurable lesion should not be biopsied and that patient is not eligible for enrollment.

6.2. Treatment Period

For treatment period procedures, see the Schedule of Activities and Assessments section (Section 7).

For the treatment period, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to, where possible:

- Pharmacokinetic blood specimens – obtain at the scheduled time.
- Electrocardiograms (ECGs) – obtain as close as possible to the scheduled time, but prior to blood specimen collection.
- Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to blood specimen collection and within 60 minutes of the nominal time.
- Clinical safety laboratory tests – obtain as close as possible to the scheduled time.
- Other procedures – All other procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection, unless sampling is determined by the study personnel to potentially impact the results.

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

6.3. Short-Term and Long-Term Follow-up

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

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

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

Patients whose disease has not progressed at the time of End of Treatment will continue to undergo disease assessments every 6 weeks (±2 days) for 1 year from the start of study treatment and then every 12 weeks (±14 days) thereafter until documented disease progression regardless of initiation of subsequent anti-cancer therapy.

6.4. 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 (see also Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (See Section 5.4.5 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to 1 or more of the investigational products, the Investigator may continue treatment with the other investigational product(s);
- Pregnancy;
- Significant protocol violation;

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

Reasons for withdrawal from study follow-up may include:

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

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

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

7. ASSESSMENTS

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

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

7.1. Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, ECG (12-lead), laboratory assessments, including pregnancy tests, and verification of concomitant treatments. See also Schedule of Activities.

7.1.1. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatments; once at the start of screening and once at the baseline visit, immediately before study drugs administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy test result will then be required at the baseline visit before the patient may receive the investigational products. Additional pregnancy tests (serum or urine) will be repeated at every treatment cycle, prior to dosing, during the active treatment period, at the end of treatment, during follow-up (for at least 90 days after the last dose of chemotherapy or for at least 30 days after last dose of avelumab, whichever is longer), and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study. See also Schedule of Activities.

Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ECs or if required by local regulations.

7.1.2. Contraceptive Check

Fertile male patients and female patients who are of childbearing potential, who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of at least one method of highly effective contraception. The Investigator or his or her designee will discuss with the patient the need to use at least 1 highly effective contraception method consistently and correctly and document such conversation in the patient's chart. In addition, the Investigator or his or her designee will instruct the patient to call immediately if the selected contraception method(s) is discontinued, or if pregnancy is known or suspected in the patient or the patient's partner. Patients who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 method of highly effective contraception throughout the study or for at least 90 days after the last dose of chemotherapy (for male and female patients) or at least 30 days after the last dose of avelumab (for female patients), whichever is longer. See also Schedule of Activities.

7.1.3. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the NCI CTCAE v4.03) timing, seriousness, and relatedness.

7.1.4. Laboratory Safety Assessments

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 14. See Schedule of Activities for details on sample timings.

Full hematology and full clinical chemistry tests must be performed. Full hematology panel as well as AST, ALT, and creatinine results must be reviewed by medically-qualified study personnel prior to each administration of study drug. Results from all other laboratory assessments are not required to be reviewed prior to study drug dosing, unless there are signs or symptoms to suggest an underlying lab abnormality. However, all lab results should be reviewed as soon as they are available.

Table 14. Laboratory Tests

Hematology	**Chemistry Panel (* denotes core chemistry test)**	**Coagulation**	**Urinalysis**	**Pregnancy Test**
Hemoglobin	ALT*	PT or INR	Protein[b]	For female patients of childbearing potential, serum or urine
Platelets	AST*	PTT	Glucose	
WBC	Alk Phosphatase*		Blood	
Absolute Neutrophils	Sodium*			
Absolute Lymphocytes	Potassium*			
Absolute Monocytes	Magnesium*			
Absolute Eosinophils	Chloride*			
Absolute Basophils	Total Calcium*			
	Total Bilirubin* [a]			
	BUN or Urea*			
	Creatinine*			
	Glucose (non-fasted)*			
	Albumin*			
Thyroid Function Tests	Phosphorous or Phosphate*			
TSH, Free T4	Total protein*			
	Uric acid			
	Amylase			
	Gamma glutamyl transferase			
	Cholesterol			
Other Tests	Creatine kinase			
ACTH	C-reactive protein			
HBV surface antigen	Lactate dehydrogenase (LDH)			
Anti-HCV antibody	Lipase			
If Anti-HCV antibody positive, then HCV RNA testing	Triglycerides			

Note: [a]For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids, and acetaminophen levels.
[b]Dipstick is acceptable. Microscopic analysis should be performed if dipstick result is abnormal. Additional tests may be undertaken if needed, at Investigator's discretion.
Abbreviations: ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, PT=prothrombin time, PTT= activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, HBV= hepatitis B Virus, HCV= hepatitis C Virus, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cell

7.1.5. Vital Signs and Physical Examination

Patients will have a physical examination to include major body systems, sitting blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the Schedule of Activities. Determination of ECOG Performance Status will continue through the 30-day Follow-Up visit unless the patient has started on a new anti-cancer therapy.

Vital signs include blood pressure and pulse rate and should be taken prior to receipt of study treatment pre-medication and all study treatment with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

Weight for the purposes of chemotherapy dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Weight will not be collected at End of Treatment.

7.1.6. (12-Lead) Electrocardiogram

All patients require triplicate ECG measurements. Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs (screening and on-treatment). On-treatment ECGs will be performed on Day 1 of Cycles 1 to 3, before administration of any study drug (including avelumab) and at the end of avelumab infusion for all patients (see Schedule of Activities). All pre-dose ECGs are to be collected prior to administration of any study drug (chemotherapy, avelumab, or any other anti-cancer immunotherapies used in future portions of the study). For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a specialist at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the Investigator(s) and Sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring as clinically indicated. If in that timeframe the QTc intervals rise above 500 msec, the investigational product(s) will be held until the QTc interval decreases to ≤500 msec. Patients will then restart the investigational product at the next lowest dose level or dose delayed as appropriate for specific investigational product. If the QTc interval has still not decreased to <500 msec after 2-weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

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

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

ECG collections should be started within a ±10% window relative to nominal time, except when coinciding with the end of avelumab infusion time, in which case ECG collection should be started within up to 10 minutes after the end of infusion. Any pre-dose ECG should be performed up to one hour prior to the start of the first infusion. ECG collections which are time-matched with PK blood samples (eg, pre-dose ECG matched with pre-dose avelumab PK blood draw) should be taken at the same time during the clinic visit. When the nominal time of an ECG coincides with a nominal time for a PK sample, the ECG must be completed before the PK sample is drawn. The PK sample should be collected as close to the nominal time as possible. If the infusion of avelumab is interrupted due to a non-cardiac or neurological AE, any ECG scheduled during the time the AE is occurring is not required.

Clinically significant new findings seen on any ECGs taken after screening should be recorded as AEs.

7.2. Pharmacokinetics Assessments

Blood samples will be obtained from all patients for PK analysis of avelumab according to the Schedule of Activities.

Blood samples for serial PK analysis of chemotherapy will be obtained as follows:

- **Cohorts A1 and A3**: Serial PK for carboplatin and pemetrexed in at least 8 patients, according to Table 2.
- **Cohorts A2 and A4**: Serial PK for cisplatin and gemcitabine in at least 8 patients, according to the Table 4.

The PK collection strategy, including nominal time points, serial versus sparse PK sampling and the number of patients, may be modified based on emerging data.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, with the exception of samples where nominal time coincides with end of infusion, samples obtained within ±30% of the nominal time (eg, within 18 minutes of a 60 minute sample) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Pre-dose PK samples should be taken on that same visit day prior to receiving any study drug, and may be grouped together (eg, pre-dose PK samples for avelumab and

chemotherapy agents are collected together at the same time before administration of the first agent).

For avelumab samples where nominal time coincides with end of infusion, a sample collected within 30 minutes post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If the infusion of avelumab is interrupted due to AE, any PK samples scheduled during the time the AE is occurring are not required.

For other study drugs where nominal time coincides with end of infusion, a sample collected within 10 min post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

All samples, regardless of protocol compliance, which contain actual time of collection will be used by the Sponsor in PK analyses. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical Investigators, patient and Sponsor.

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

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

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

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7.2.1. All Groups: Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood at each time point) will be collected for PK analysis of avelumab into appropriately labeled serum separator tube (SST) as outlined in the Schedule of Activities. PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

7.2.2. All Groups: Blood for PK Analysis of Chemotherapies

PK sampling schedules may be modified based on emerging PK data.

7.2.2.1. Cohorts A1 and A3: Blood for PK Analysis of Carboplatin

Blood samples (3 mL whole blood at each time point) will be collected into appropriately labeled tubes containing K_2 ethylenediaminetetraacetic acid (EDTA) for PK analysis of carboplatin (free and total platinum) as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

7.2.2.2. Cohorts A1 and A3: Blood for PK Analysis of Pemetrexed

Blood samples (2 mL whole blood at each time point) will be collected into appropriately labeled tubes containing K_2EDTA for PK analysis of pemetrexed as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

7.2.2.3. Cohorts A2 and A4: Blood for PK Analysis of Gemcitabine

Blood samples (3 mL whole blood at each time point) will be collected into appropriately labeled tubes containing K_2EDTA for PK analysis of gemcitabine (and its metabolite, 2',2'-difluorodeoxyuridine [dFdU]) as outlined in the Schedule of Activities. Blood samples will be pretreated with tetrahydrouridine (THU) to inhibit ex vivo conversion of gemcitabine to dFdU. Detailed instructions on the preparation and use of THU will be provided in the lab manual. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

7.2.2.4. Cohorts A2 and A4: Blood for PK Analysis of Cisplatin

Blood samples (3 mL whole blood at each time point) will be collected into appropriately labeled tubes containing K_2EDTA for PK analysis of cisplatin (free and total platinum) as outlined in the Schedule of Activities. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

7.3. Immunogenicity Assessments

Blood samples (3.5 mL whole blood) will be collected for assessment of avelumab ADAs into an appropriately labeled serum separator tube (SST). Pre-dose ADA samples will be collected within 2 hours prior to the first drug administration of the day (when multiple agents are dosed on the same day). Further details can be found in the Lab Manual. This assessment will take place at regular intervals during the treatment and follow-up periods as described in the Schedule of Activities.

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

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

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

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

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7.4. Biomarker and Pharmacodynamic Assessments

Information about the following tumor biomarkers of known prognostic significance will be collected at Screening.

- NSCLC:
  - EGFR and ALK required to be collected for patients with non-squamous NSCLC.
  - KRAS, ROS1, and PD-L1 collected if available for patients with non-squamous NSCLC.
- UC: PD-L1 collected if available.

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers in tissue and blood that may have predictive value in identifying those patients who are most likely to benefit from treatment with the combination of avelumab and chemotherapy with or without other immunotherapies. In addition, analyses of biomarkers in paired pre- and post-treatment biopsies and of sequentially obtained blood samples will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment visit may help us understand potential acquired mechanisms of resistance to the drug combination.

7.4.1. Archived Tumor Biospecimens and De Novo Tumor Biopsies

Baseline tumor biospecimens (see Section 6.1.1) will be used to analyze candidate DNA, RNA, and/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.

These markers will also be analyzed in on-treatment biopsies in order to assess pharmacodynamic and mechanistic biomarkers that may inform dose selection and activity.

Candidate markers of interest include the mutational and neoantigen load of tumors as determined by DNA sequencing at baseline and PD-L1 expression on/in tumor and infiltrating immune cells measured by IHC at baseline and on-treatment.

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Optional tumor biopsies obtained upon disease progression may be used to assess the same, or additional, markers with the aim of determining any acquired mechanisms of resistance. Additional information on tissue collection procedures can be found in Section 6.1.1 and the Study Manual.

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[redacted]

7.6. Tumor Response Assessments

Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned depending upon malignancy are detailed in the Imaging Manual. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans. For patients with NSCLC (Cohorts A1 and A3), pelvic assessments will be conducted only if clinically indicated at baseline or at any subsequent point. Patients with cisplatin-eligible UC (Cohorts A2 and A4) should have chest, abdomen, and pelvis CT or MRI scans. Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom CNS involvement is suspected. If stable brain metastases are present at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

Whole body bone imaging using bone scan (bone scintigraphy) (preferred method) or other methods considered standard of care locally such as 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET), ^{18}F-sodium fluoride-PET (^{18}F- NaF-PET), PET/CT, CT, or MRI is required at baseline. Bone lesion(s) identified at baseline by bone scintigraphy, ^{18}F-FDG-PET, ^{18}F- NaF-PET, or PET/CT will be further assessed by correlative imaging, such as diagnostic CT or MRI as per local practice (where bone scans are not used as a routine restaging tool) and subsequently re-assessed by diagnostic CT or MRI as per the tumor assessment schedule. Only for those patients with bone lesions present at baseline, whole body bone imaging should be repeated at every other tumor assessment visit (ie, every 12 weeks during the first 12 months of study treatment and every 24 weeks thereafter) and at the time of confirmation of CR. For all patients, whole body bone imaging may be repeated during study as clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level or other signs and symptoms of new/progressing bone metastases).

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

The CT and MRI scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, then every 6 weeks (±2 days) for 1 year from start of study treatment, and then every 12 weeks (±14 days) thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities. In addition, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

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

Assessment of response will be made using RECIST v1.1 (Appendix 3). Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

In case CR or PR is observed, tumor assessments must be confirmed on repeated imaging at least 4 weeks after initial documentation. See Section 5.4.5 for treatment after initial evidence of disease progression.

All patients' files and radiologic images must be available for source verification and for potential peer review. All radiographic images will be collected and stored by an independent third-party imaging laboratory.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

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

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

8.1.1. Additional Details On Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

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

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

This section describes the data analysis and statistical methods for each of the combinations and cohorts evaluated in this study.

9.1. Analysis Sets

9.1.1. Full Analysis Set

For each cohort, the full analysis set includes all enrolled patients in the cohort who receive at least 1 dose of study drug. Each patient will be classified according to the first treatment combination received.

9.1.2. Safety Analysis Set

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

9.1.3. Evaluable for DLT Analysis Set

The DLT analysis set is a subset of the safety analysis set and includes all enrolled patients in Phase 1b lead-in who are eligible for the study, receive at least one dose of the combination treatment, and either experience DLT during the first 2 cycles of treatment, or complete the DLT observation period for the first 2 cycles of treatment.

Patients without DLTs who withdraw from study treatment before receiving, over 2 cycles, at least 75% of the prescribed doses of avelumab and each relevant chemotherapy for reasons other than treatment-related toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

9.1.4. Pharmacokinetics Analysis Sets

The PK concentration analysis sets (one unique set for each individual agent used in study treatment) are subsets of the safety analysis set including all treated patients who have at least one post-dose concentration measurement above the limit of quantitation of avelumab or other study drugs which they were assigned to receive, based on the cohort.

The PK parameter analysis sets (one unique set for each individual agent used in study treatment) are subsets of the safety analysis set including all treated patients who have at least one PK parameter of interest of avelumab or the other study drugs which they were assigned to receive, based on the cohort.

9.1.5. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set including all treated patients who have at least one ADA sample collected.

9.1.6. Biomarker Analysis Set

For all combinations, the biomarker analysis set is a subset of the safety analysis set including all treated patients who have at least one screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

If mutational profiling is performed on samples derived from the biomarker analysis set, the analysis may be limited to screening samples only.

9.2. Statistical Methods and Properties

Phase 1b lead-in: Before expanding each cohort into the Phase 2 cohort expansion, the safety of the combination in a cohort must be confirmed in DLT-evaluable patients in the Phase 1b lead-in.

Up to 12 patients will be enrolled into each cohort in the Phase 1b lead-in and evaluated for DLT during the first 2 cycles of treatment as follows.

Cohorts A1 and A2

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:
    - If ≤1 of 6 patients experience DLT in Cohort A1 (or A2), enrollment may be initiated in Phase 1b Cohorts A3 (or A4);
    - If ≥3 of up to 6 patients experience DLT in Cohort A1 (or A2), enrollment in Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination;
    - If 2 of 6 patients experience DLT in Cohort A1 (or A2), the cohort will be expanded to enroll up to 6 additional DLT-evaluable patients in the Phase 1b Cohort A1 (or A2):
        - If ≤3 of 12 patients experience DLT in Cohort A1(or A2), enrollment may be initiated in Phase 1b Cohort A3 (or A4);
        - If ≥4 of up to 12 patients experience DLT in Cohort A1 (or A2), enrollment in Cohort A1 (or A2) will be discontinued; there will be no further enrollment of patients with the combination.

Cohorts A3 and A4

- Enroll and treat up to 6 DLT-evaluable patients in each cohort:
  - If ≤1 of 6 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy;
  - If ≥3 of up to 6 patients experience DLT in Cohort A3 (or A4), enrollment in the Cohort A3 (or A4) will be discontinued; enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;
  - If 2 of 6 patients experience DLT in Cohort A3 (or A4), the Cohort A3 (or A4) will be expanded to enroll up to 6 additional DLT-evaluable patients;
    - If ≤3 of 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A3 (or A4) expansion with the study treatment of avelumab 1200 mg Q3W in combination with chemotherapy; there will not be any enrollment in Phase 2 Cohorts A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy;
    - If ≥4 of up to 12 patients experience DLT in Cohort A3 (or A4), enrollment may be initiated in Phase 2 Cohort A1 (or A2) expansion with the study treatment of avelumab 800 mg Q3W in combination with chemotherapy.

Table 15 shows the probability of meeting DLT requirements to escalate to dose level of avelumab 1200 mg Q3W in combination with chemotherapy. For example, for a DLT that occurs in 10% of patients, the probability of confirming safety and escalating to avelumab 1200 mg Q3W is approximately 0.97.

As per the DLT criteria, if the dose level of avelumab is escalated to 1200 mg, Phase 2 cohort expansion may be initiated with the study treatment of avelumab, either 800 mg Q3W or 1200 mg Q3W, in combination with chemotherapy.

Table 15. Probability of Escalating Dose Level of Avelumab to 1200 mg Q3W after Phase 1b Lead-in of Each Cohort (A1 and A2)

True underlying DLT rate*	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose level of avelumab	0.97	0.82	0.56	0.31	0.14	0.05	0.01	0.002	<0.0001

*True underlying DLT rate for the combination of avelumab 800 mg Q3W with chemotherapy.

9.3. Sample Size Determination

The number of patients to be enrolled in the Phase 1b lead-in may depend upon the observed safety profile, which will determine the number of patients enrolled in each cohort. The total number of patients in the Phase 1b lead-in is expected to be up to 48 (up to 12 patients per cohort).

If investigational products administration the Phase 1b Lead-in portion of a given cohort is deemed safe based on the criteria described in "Phase 1b Lead-in" Section 3.1, then enrollment into that cohort may continue into the Phase 2 Cohort Expansion. The dose of avelumab to be administered in the Phase 2 Cohort Expansion (800 mg Q3W for Cohorts A1 and A2 or 1200 mg Q3W for Cohorts A3 and A4) will be determined based on the number of observed DLTs as described in "Phase 1b Lead-in" Section 3.1. The highest dose level of avelumab deemed safe for the combination will be advanced.

Based on safety data for patients with cisplatin-eligible UC, the Phase 1b lead-in from either Cohort A2 (800 mg avelumab plus chemotherapy) or cohort A4 (1200 mg avelumab plus chemotherapy) may be selected to continue enrollment into the Phase 2 cohort expansion. Up to approximately 40 patients with cisplatin-eligible UC, including Phase 1b lead-in and Phase 2 cohort expansion patients, may receive the selected avelumab dose plus chemotherapy.

Based on safety data for patients with non-squamous NSCLC, the Phase 1b lead-in from either Cohort A1 (800 mg avelumab plus chemotherapy) or Cohort A3 (1200 mg avelumab plus chemotherapy) may be selected to continue enrollment into the Phase 2 cohort expansion. Up to approximately 20 patients with non-squamous NSCLC, including Phase 1b lead-in and Phase 2 cohort expansion patients, may receive the selected avelumab dose plus chemotherapy.

In future portions of the study, up to approximately 40 patients in each cohort (including those enrolled in Phase 1b lead-in and those enrolled in Phase 2) will be enrolled and treated with avelumab plus chemotherapy with or without other anti-cancer immunotherapies. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

With 40 patients with cisplatin-eligible UC and 20 patients with non-squamous NSCLC in Phase 1b and Phase 2 combined, ORR can be estimated with a maximum standard error of 0.079 and 0.112, respectively. Within each cohort, ORR will be estimated and the two-sided exact 90% confidence interval will be calculated. Table 16 provides the exact binomial 90% confidence intervals for ORR based on different observed responses in a cohort.

Table 16. Sample Size and Exact 90% CI for ORR in each Cohort

N per Cohort	Number of Responders	Observed ORR	90% CI for ORR
20	1	5%	(0.3% – 21.6%)
	2	10%	(1.8% – 28.3%)
	3	15%	(4.2% – 34.4%)
	4	20%	(7.1% – 40.1%)
	5	25%	(10.4% – 45.6%)
	6	30%	(14.0% – 50.8%)
	7	35%	(17.7% – 55.8%)
	8	40%	(21.7% – 60.6%)
	9	45%	(25.9% – 65.3%)
	10	50%	(30.2% – 69.8%)
	12	60%	(39.4% – 78.3%)
	15	75%	(54.4% – 89.6%)
40	2	5%	(0.9% – 14.9%)
	4	10%	(3.5% – 21.4%)
	6	15%	(6.7% – 27.5%)
	8	20%	(10.4% – 33.2%)
	10	25%	(14.2% – 38.7%)
	12	30%	(18.3% – 44.0%)
	14	35%	(22.6% – 49.2%)
	16	40%	(26.9% – 54.2%)
	18	45%	(31.5% – 59.1%)
	20	50%	(36.1% – 63.9%)
	24	60%	(45.8% – 73.1%)
	30	75%	(61.3% – 85.8%)
	35	87.5%	(75.5% – 94.9%)

CI=confidence interval; ORR=objective response rate

9.4. Efficacy Analysis

All efficacy analyses will be performed for each cohort separately including all patients in the full analysis set from the Phase 1b lead-in and the Phase 2 cohort expansion parts combined.

9.4.1. Analysis of the Primary Endpoint

The primary endpoint for Phase 1b lead-in and the Phase 2 cohort expansion combined is the confirmed objective response (OR) as assessed by the Investigator using RECIST v1.1.

OR is defined as a CR or PR per RECIST v1.1 from the first dose of study treatment until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Objective response rate (ORR) is defined as the proportion of patients with a confirmed CR or PR per Investigator's assessment according to RECIST v.1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow up assessments) will be considered as non-responders in the assessment of ORR. The two-sided exact 90% CI for ORR will be calculated.

9.4.2. Analysis of the Secondary Endpoints

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

Duration of Response (DR) is defined for patients with confirmed objective response (CR or PR) as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. Censoring for DR will follow that described below for PFS.

Progression-Free Survival (PFS) is defined as the time from the first dose of study treatment to the date of disease progression by RECIST v1.1 or death due to any cause, whichever occurs first. PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after 2 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 date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment in which case the death will be considered an event.

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

TTR will be summarized using simple descriptive statistics (eg median and range). DR, PFS, and OS will be analysed using Kaplan-Meier methods and descriptive statistics. Point estimates will be presented with their 90% and 95% confidence intervals. In addition, progression date, death date, date of first response, and last tumor assessment date will be listed, together with best overall response (BOR), TTR, DR, and PFS.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. Analysis of Pharmacokinetics of Study Drugs

Serum pharmacokinetic parameters including the maximum serum concentration (C_{max}), trough serum concentration (C_{trough}), and area under the concentration versus time curve (AUC_{last}, AUC_{τ}) for avelumab will be estimated using non-compartmental analysis, if data permit.

Plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}), trough plasma concentrations (C_{trough}), and area under the plasma concentration versus time curve (AUC_{last}, AUC_{τ}) for chemotherapy (carboplatin [free and total platinum], pemetrexed, gemcitabine [including metabolite dFdU], and cisplatin [free and total platinum]) will be estimated using non-compartmental analysis, if data permit.

The single-dose and/or multiple-dose/ steady-state PK parameters will be summarized descriptively by cycle, day (if applicable), and dose (if applicable). Dose-normalized (DN) parameters (eg, DN-C_{max}, DN-C_{trough}, DN-AUC) will be reported as appropriate.

Avelumab, chemotherapy (carboplatin [free and total platinum], pemetrexed, gemcitabine [including metabolite dFdU], and cisplatin [free and total platinum]) concentrations will be summarized descriptively (n, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, maximum, geometric mean and its associated CV) by cycle, day, nominal time and dose (if applicable). Individual patient and median profiles of the concentration-time data will be plotted by cycle, day (if applicable), and dose (if applicable) using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

The pharmacokinetic interaction potential of each drug will be evaluated in an exploratory manner based on overall assessment of the geometric mean ratios for exposure parameters (eg, C_{max}, area under the curve to the end of the dosing period [AUC_{tau}]) of each drug at single-dose and/or multiple-dose/steady-state in comparison to those PK parameters obtained from the monotherapy or appropriate combination settings. Comparison will be made to historical PK data and presented descriptively, if data permit.

9.5.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

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

9.5.3. Analysis of Immunogenicity Data of Avelumab and Other Study Drugs

Anti-drug antibody (ADA) and neutralizing antibody (nAb) data will be listed and summarized for each dosing interval for avelumab. The percentage of patients with positive ADA and neutralizing antibodies each will be summarized across the study and by cohort. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. The effect of ADA on avelumab concentrations will be evaluated.

9.6. Biomarker Analyses for Secondary CCI [redacted] Endpoints

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

For discrete measurement biomarkers, frequencies and percentages of categorical biomarker measures will be determined at baseline and on-treatment/end of treatment time points.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics. The statistical approaches will examine correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

9.7. Safety Analysis

Safety analysis will be performed on the safety analysis set in the study for each combination and cohort for Phase 1b lead-in and for all patients in the Phase 1b lead-in and Phase 2 cohort expansion parts combined.

9.7.1. Analysis of the Primary Endpoint in the Phase 1b Lead-in

DLT is the primary endpoint of the Phase 1b lead-in part of the study for all cohorts evaluated.

Analyses of DLT are based on the DLT-evaluable set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed per cohort for patients in the Phase 1b lead-in.

9.7.2. Analysis of Secondary Safety Endpoints

9.7.2.1. Adverse Events

AEs will be graded by the Investigator according to the CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on TEAE, those with initial onset or increasing in severity after the first dose of study treatment. The number and percentage of patients who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades.

9.7.2.2. Laboratory Test Abnormalities

The laboratory results will be graded according to the CTCAE v4.03 severity grade whenever applicable. The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory test.

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

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

9.7.2.3. Electrocardiograms

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline ECG is defined as the ECG performed on Day 1 of Cycle 1 prior to any study drug treatment.

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

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS and QTc. Individual QT (all evaluated corrections) intervals will be listed by combination, cohort, time point and dose (if applicable). The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by combination, cohort, time point, and dose (if applicable). The maximum change from baseline will be calculated as well as the maximum post-baseline interval across time points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline versus worst on-treatment corrected QT (one or more correction method will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline versus on-treatment (yes, no, not done: (n, %)). Patients experiencing clinically-relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.8. 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.

9.9. Data Safety Monitoring Committee

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another Investigator, another institution, or 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 the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Patient Information and Consent

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

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

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

The informed consent document(s) used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/Independent Ethics Committee (IEC) before use, and available for inspection.

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the

CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of avelumab or other anti-cancer immunotherapies used in future portions of the study at any time. For the UK and the Czech Republic: Only 1 additional anti-cancer immunotherapy, in combination with avelumab and chemotherapy, in up to 4 tumor-specific cohorts, will be included.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. Abbreviations and Definitions of Terms

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

^{18}F-FDG-PET	18-Fluorodeoxyglucose Positron Emission Tomography
^{18}F-NaF-PET	Fluorine 18 Sodium Fluoride Positron Emission Tomography
ADA	Anti-Drug Antibody
ADL	Activities of Daily Life
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CCI	[redacted]
BID	Twice-Daily
BNP	B-Type Natriuretic Peptide
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
C_{avg}	Average plasma concentration
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase – Muscle and Brain Subunits
CL	Clearance
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
C_{trough}	Lowest (trough) Concentration
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
ct	Circulating Tumor
CT	Clinical Trial
CT	Computerized Tomography
CTA	Clinical Trial Application
CTLA-4	Cytotoxic T Lymphocyte-Associated Protein 4
CTCAE	Common Terminology Criteria for Adverse Events (US NCI)
CV	Coefficient of Variation
CYP	Cytochrome P450
DAI	Dosage and Administration Instructions
DDI	Drug-Drug Interaction
dFdU	Difluorodeoxyuridine
DILI	Drug-Induced Liver Injury
DLBCL	Diffuse Large B Cell Lymphoma

DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
DU	Dispensible Unit
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDP	Exposure During Pregnancy
EDTA	Ethylenediaminetetraacetic Acid
EGFR	Epidermal Growth Factor Receptor
EU	European Union
EudraCT	European Clinical Trials Database
F	Farenheit
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin Fixed, Paraffin Embedded
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl Transferase
GH	Growth Hormone
GITR	Glucocorticoid Induced TNF Receptor
GMP	Good Manufacturing Practice
GVHD	Graft versus Host Disease
HA	Hyaluronic Acid
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDPE	High-Density Polyethylene
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
hr	hour
hrs	hours
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% Inhibitory Concentration
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IFN	Interferon
Ig	Immunoglobulin
IGF-1	Insulin-Like Growth Factor-1
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product

IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IWR	Interactive Web-Based Response
LAG3	Lymphocyte Activation Gene 3
LFT	Liver Function Test
LH	Luteninizing Hormone
mAb	Monoclonal Antibody
MCC	Merkel Cell Carcinoma
MDSC	Myeloid Derived Suppressor Cell
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Compex
MHRA	Medicines and Healthcare products Regulatory Agency
MOA	Monamine Oxidase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mRNA	Messenger Ribonucleic Acid
MVAC	Methotrexate/Vinblastine/Doxorubicin/Cisplatin
N/A	Not Applicable
nAb	Neutralizing Antibody
NE	Not Evaluable
NCI	National Cancer Institute
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression-Free Survival
PK	Pharmacokinetics
PO	By Mouth (Oral Administration)
PR	Partial Response
PRL	Prolactin
PS	Performance Status
PT	Preferred Term
PT	Prothrombin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QD	Once Daily
RCC	Renal Cell Carcinoma

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBLA	Supplemental Biologics Application
SC	Subcutaneous
SD	Stable Disease
SRSD	Single Reference Safety Document
SST	Serum Separator Tube
SUKL	Czech Republic State Institute for Drug Control
$t_{½}$	Terminal Half-Life
T4	Free Thyuroxine
TBili	Total Bilirubin
TCR	T-cell Receptor
TEAE	Treatment Emergent Adverse Event
TGF	Tumor Growth Factor
TGI	Tumor Growth Inhibition
THU	Tetrahydrouridine
TIL	Tumor Infiltrating Lymphocytes
TIM3	T cell immunoglobulin and mucin
TKI	Tyrosine Kinase Inhibitor
TNF	Tumor Necrosis Factor
TO	Target Occupancy
TPS	Tumor Proportion Score
Treg	Regulatory T cell
TSH	Thyroid Stimulating Hormone
TTR	Time to Tumor Response
UC	Urothelial Cancer
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USPI	United States Prescribing Information
v	Version
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2. ECOG Performance Status

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

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

Appendix 3. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Guidelines

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[49]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and <15 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

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

Normal sites

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

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

RECORDING TUMOR ASSESSMENTS

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

Target Lesions

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

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

- Measurements for target lesions that become small should continue to be recorded. If the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate "too small to measure and judged to be less than 10 mm" and 5 mm will be used in the calculation of the sum of the diameters.

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

Non-target Disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target Disease

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

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir (smallest sum of diameters consider baseline and all assessments prior to the time point under evaluation), but enough that a previously documented 30% decrease no longer holds.

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

- Not evaluable (NE): Progression has not been documented; and

    - one or more target lesions have not been assessed; or

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

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

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

Non-target Disease

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

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

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

- Not evaluable (NE): Progression has not been determined and:

    - one or more non-target lesion sites have not been assessed; or

- assessment methods used were inconsistent with those used at baseline; or
- one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images); or
- one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

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

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

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

Determination of Tumor Response by RECIST

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

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

Target Lesions	Non-target Lesions	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD or not all evaluated	No	PR
PR	Non-PD* or not all evaluated	No	PR
SD	Non-PD* or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes**	PD

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

Determination of Best Overall Response

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

Appendix 4. Calculation of Carboplatin Dose Based on Calvert Formula

The carboplatin dose should be calculated according to the Calvert[40] formula as follows:

- Carboplatin dose = Target AUC x (GFR + 25).
- Maximum Carboplatin Dose (mg) = target AUC (mg·min/mL) x (150 mL/min).

The maximum dose is based on a glomerular filtration rate (GFR) estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

The GFR should be calculated as per local practice.

GFR Limitations

- Isotopic GFR is inaccurate in patients with significant effusions, ascites or edema as the isotope distributes into third space fluid collections.
- Patients who have had complicated or prolonged post-operative recovery and who have been maintained on prolonged IV fluids with poor nutrition will have a falsely low serum creatinine.
- Formulae, such as the Cockroft-Gault formula, are inaccurate at the extremes of age and weight. The calculated GFR may be falsely high in obese young women and falsely low in thin elderly women.
- It is assumed that clinicians entering patients into this protocol will be aware of these issues and the clinical judgment of an experienced clinician should be applied to the calculation of the carboplatin dose.

The dose of carboplatin should be recalculated prior to each infusion unless the isotopic method is used, in which case, the dose should be recalculated if the creatinine rises above 1.5 X ULN.