JAVELIN CHEMOTHERAPY MEDLEY

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

STATISTICAL ANALYSIS PLAN – B9991023

Compounds:	MSB0010718C
Compound Name:	Avelumab
Version:	2.0
Date:	10-Feb-2021

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991023 is based on the protocol amendment 04 dated 02OCT2018.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
1	09 Aug 2017	Not applicable (N/A)
2	10 Feb 2021	The following changes in the SAP were implemented in accordance to protocol amendment 4. CCI [redacted] • Section 2.2 "Study Design", Section 3.4.1 "Study drug, study treatment and baseline definitions", Section 5.1.1 "Hypotheses and sample size determination" and Section 5.2 "General Methods" - introduction of 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. • Section 5.1.1 "Hypotheses and sample size determination" – added the rows for 20 patients in Table 4 "Sample Size and Exact 90% CI for ORR in each treatment group" to account for the reduction of the target number of patients with non-squamous NSCLC in Phase 1b + Phase 2 combined. • Section 0 "Decision rules" – updated the Table 5 to show the probability of escalating dose level of avelumab to 1200 mg Q3W in Cohorts A3 and A4 after the Phase 1b lead-in (Cohorts A1 and A2), instead of the probability of expanding Phase 1b lead-in. In addition, the following changes were implemented. • Section 3.2.3. "Pharmacokinetic endpoints" – Table 2 of the PK parameters was simplified. • Section 3.4.2. "Baseline characteristics", Section 5.2.8. "Standard derivations and reporting conventions", Section 6.5.1.1. "Demographic characteristics" – the summary of physical measurements (BMI, height and weight) was deleted. • Section 3.5.1 and Section 6.6.1 "Adverse events" – updated definition of treatment-emergent adverse events to include only adverse events with onset dates during the on-treatment period. • Section 4.3.1 "DLT-evaluable set" – clarified the definition of DLT-evaluable set using the number of doses as criteria of "at least 75% intended dose". • Section 4.3.2 "PK analysis sets" – updated the definition of PK analysis sets. • Section 5.1.1. "Hypotheses and sample size determination" – the Phase 1b Lead-in dose escalation rules were removed and a reference to Section 2.2. was added.

		• Section 5.3.2 "Handling of incomplete dates" for PK and Immunogenicity data was removed because no imputation will be done for unknown or partially unknown dates. • Section 5.3.2.5 "Date of last contact" – added withdrawal of consent date in the derivation of date of last contact. • Section 5.3.2.8 "Date of start of new anti-cancer therapy" – added details of imputation rules for incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery). • Section 6.1.2.1. "Primary analysis" – removed 2-sided 90% CI for ORR. • Section 6.2.2.2 "Duration of response" – added details regarding censoring for duration of response since "no adequate baseline assessment" and "no adequate post-baseline assessment" which is used in censoring for PFS analyses is not applicable to analyses of duration of response for patients with objective response. The listing of duration of response time was deleted. • Section 6.2.2.2 "Duration of response", Section 6.2.2.4 "Progression-free survival" and Section 6.2.2.5 "Overall survival" – added additional landmark analyses of probability of being event-free "every 3 months as appropriate" to represent longer responses. • Section 6.2.2.4. "Progression-free survival" - the summary of time of follow-up for PFS was simplified. • Section 6.2.2.5. "Overall survival" - the summary of time of follow-up for OS was simplified. • Section 6.2.5 "Biomarker endpoints" – removed the descriptive summary statistics because only the categorical data are available; removed the summary for OS for each biomarker category. CCI [redacted] • Section 6.2.6 "Endpoints for immunogenicity data of avelumab" – added details for the analysis of ADA and nAB. CCI [redacted] • Section 6.4 "Subset Analyses" – removed subset analyses for the following variables based on clinical importance and number of patients expected in the subgroups: duration of response, ECOG performance score, adenocarcinoma type in NSCLC cohorts. • Section 6.5.1.3 "Disease characteristics" – removed summary of substance use. • Section 6.5.1.4 "Prior anti-cancer therapies" – removed summary by drug class. The data will be included in the listing of anti-cancer therapies with a flag to identify prior therapies. • Section 6.5.1.4. "Prior anti-cancer therapies", Section 6.5.5. "Subsequent anti-cancer therapies" - the listings of anti-cancer radiation therapy and anti-cancer surgeries were deleted. • Section 6.5.2.2. "Protocol deviations" – Incorrect dose was removed. • Section 6.5.3 "Study treatment compliance and exposure" - removed by-cycle summaries. • Section 6.5.4 "Concomitant medications and non-drug treatments" – removed summary tables of prior medications, pre-medications and

		non-drug treatments. The listings of prior medications, concomitant medications, pre-medications and non-drug treatments were deleted. • Section 6.5.5 "Subsequent anti-cancer therapies" - removed summary by type of therapy. The data will be included in the listing of anti-cancer therapies. • Section 6.6.1 "Adverse events" and subsections – added summaries of adverse events leading to dose reduction of each chemotherapy, and summaries of adverse events leading to interruption of each study drug. The following summaries were removed: all immune-related AEs (irAEs), irAEs leading to death, irAEs of Grade ≥ 3, all infusion related reactions (IRRs), IRRs leading to death, IRRs of Grade ≥ 3, time related to first onset of an IRR, treatment-related AEs leading to discontinuation of each study drug, any and all study drugs. • Section 6.6.5 "Laboratory data" and subsections – removed descriptive summaries by visit as data will be summarized based on newly occurring or worsening laboratory abnormalities. Laboratory test results with no CTCAE criteria will not be summarized. • Section 6.6.5.2. "Other laboratory parameters" - the listing of abnormal values of laboratory results was removed. • Section 6.6.6 "Vital Signs" – removed summary and listing. • Section 6.6.7 "Electrocardiogram" – removed by-cycle summaries and listings. The study-specific QT correction for heart rate (QTcP) has been deleted from the SAP. • Section 6.6.8 "Physical Examination" was removed as data not collected in the eCRF • Section 6.6.9 "ECOG performance status" – removed the ECOG shift table. • Appendix 1 "Immune-Related Adverse Events" – updated the definition of irAEs in Table 14 with steps 3 and 4 of the algorithm to be checked concurrently. Redundant listings or listings that do not provide meaningful information were removed. Minor editorial and consistency changes throughout the document.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991023. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (i.e., pharmacokinetics [PK] data, immunogenicity data, biomarker data). The primary analysis will include all data up to a clinical cut-off date corresponding to 18 months after the last patient receives the first dose of study drug. The final analysis of the data will be performed after last patient last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives

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 objective response rate (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-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.

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2.2. Study Design

This is a Phase 1b/2, open-label, multi-center, safety, clinical activity, PK, and pharmacodynamics study of avelumab in combination with chemotherapy, 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 non-small cell lung cancer (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.

Avelumab in combination with chemotherapy (Group A) will be evaluated as follows:

- 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.

Patients are not allowed to cross over between the different combinations evaluated in this study.

Each combination will be studied in 2 phases:

- a Phase 1b lead-in to evaluate preliminary safety of the combination;
- a Phase 2 cohort expansion to evaluate preliminary efficacy and further evaluate safety.

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 defined above 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 experiences 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 (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.

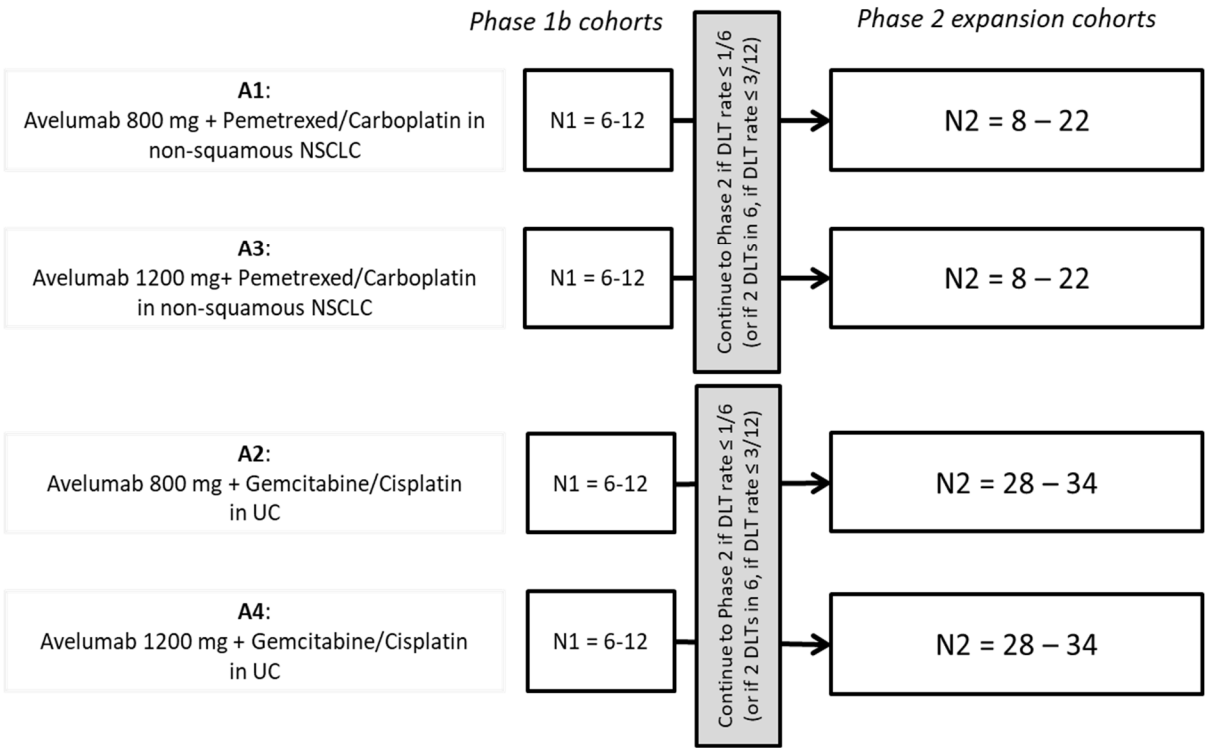
For the cohort of patients with cisplatin-eligible UC selected to expand to Phase 2, up to approximately 40 patients, including those enrolled in Phase 1b Lead-in and those enrolled in the Phase 2 Cohort Expansion, will be treated with the combination of avelumab and chemotherapy with or without other 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.

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 progressive disease 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.

Figure 1 Study Design Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Phase 1b lead-in: First 2 cycles DLT.

  Severity of adverse events will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Any of the following adverse events (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 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.

- Confirmed objective response (OR), as assessed by the Investigator using RECIST v1.1.

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first dose of study treatment until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- AEs as characterized by type, severity (as graded by National Cancer Institute [NCI] CTCAE v.4.03), timing, seriousness, and relationship to study treatments;

  AEs will be graded by the investigator according to the NCI CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

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

3.2.2. Efficacy endpoints

- Time-to-event endpoints including progression-free survival (PFS), duration of response (DR), time to tumor response (TTR), as assessed by the Investigator using RECIST v1.1; and overall survival (OS);

  DR is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

  TTR is defined, for patients with an OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

  PFS is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

  OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause.

3.2.3. Pharmacokinetic endpoints

- PK parameters of avelumab;

- PK parameters of chemotherapies, as data permit.

  Serum PK parameters of avelumab will be reported including but not limited to C_{max} and C_{trough} after single dose and at multiple dose/steady state. PK parameters of chemotherapies will be reported as data permit, including but not limited to C_{max}, C_{trough}, T_{max}, $AUC_{ss,\tau}$, and AUC_{last} following multiple dosing.

Dose-normalized (dn) parameters will be reported as appropriate.

Table 2. PK Parameters to be Determined for Avelumab and Chemotherapy[a]

Parameter	Definition	Method of Determination
AUC_{last} [b]	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}) for chemotherapy	Linear/Log trapezoidal method
$AUC_{ss, \tau}$ [b]	Area under the plasma concentration-time profile from time zero to the next dose (after multiple doses)	Linear/Log trapezoidal method
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
$AUC_{ss, \tau}(dn)$[b]	Dose normalized $AUC_{ss, \tau}$	$AUC_{ss, \tau}$ / Dose
$C_{max}(dn)$	Dose normalized C_{max}	C_{max} / Dose
$C_{trough}(dn)$	Dose normalized C_{trough}	C_{trough} / Dose

[a] Chemotherapy includes carboplatin, cisplatin, gemcitabine, pemetrexed (including any bioanalytically-quantified analytes associated with the drug as applicable, e.g. metabolites, or free and total forms of drug)
[b] if data permit.

3.2.4. Immunogenicity endpoints

- Anti-drug antibody (ADA) levels;

  The presence of ADA / Neutralizing antibodies (nAb) for avelumab when used in combination with chemotherapy (in Cohorts A1 and A2).

3.2.5. Biomarker endpoints

- Mutational load within baseline tumor tissue.

- PD-L1 expression in baseline and on-treatment tumor tissue.

Table 3. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
Mutational load within baseline tumor tissue	The total number or number per megabase of the genome, coding, base substitution, and indel mutations present in the sample.	Next generation sequencing followed by computational analysis.
PD-L1 expression at baseline and on treatment	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest	Pathologist, assisted by image analysis.

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3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to avelumab, and chemotherapies (carboplatin, cisplatin, gemcitabine, pemetrexed), and '**study treatment**' (or '**treatment group**') refers to one of the following:

- 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.

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for efficacy analyses and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or

is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit). Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and 0, respectively.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

The full analysis set (FAS) will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first study treatment received.

4.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one study treatment, the patient will be classified according to the first study treatment received. In this non-randomized study, the FAS and the safety analysis set are identical.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

The DLT analysis set is a subset of the safety analysis set and includes all enrolled patients in the 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 (6 weeks) 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 at least 75% of the prescribed doses for 2 cycles for all investigational products in the combination for reasons other than treatment-related toxicity (eg, missed appointments or development of rapidly progressing disease, consent withdrawal) are not evaluable for DLT. To meet the criteria of "at least 75% intended dose", the patient must have received at least 2 of the 2 intended doses for each study drug except gemcitabine, or 3 of the 4 intended doses for gemcitabine during the DLT observation period.

4.3.2. PK analysis sets

The PK concentration analysis sets (one unique set for each study drug used in the combination treatment) are subsets of the safety analysis set including patients who have at least one concentration measurement for avelumab or other study drugs (including any bioanalytically-quantified analytes associated with the drug, e.g. metabolites, free and total forms of drug, or enantiomers) which they were assigned to receive, based on the treatment group.

The PK parameter analysis sets (one unique set for each study drug used in the combination treatment) are subsets of the safety analysis set including patients who have at least one PK

parameters of interest for avelumab or the other study drugs (including any bioanalytically-quantified analytes associated with the drug, e.g. metabolites, free and total forms of drug, or enantiomers) which they were assigned to receive, based on the treatment group.

4.3.3. Biomarker analysis sets

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

For the analysis of tumor tissue-based biomarkers in paired biopsies, the analysis set is a subset of the safety analysis set including patients who have at least one baseline and one on-treatment biomarker assessment for the same biomarker.

4.3.4. Immunogenicity analysis set

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

Phase 1b lead-in

There is no formal hypothesis testing in this phase. However, 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 treatment group in the Phase 1b lead-in and evaluated for DLT during the first 2 cycles of treatment as follows (see Section 2.2 Phase 1b Lead-in).

Phase 2

In Phase 2 enrollment in each treatment group will be expanded to a total of up to approximately 40 patients (including those enrolled in Phase 1b lead-in and those enrolled in Phase 2).

Phase 1b and 2 combined

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 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. Table 4 provides the exact binomial 90% confidence intervals (CIs) for ORR based on different observed responses in a treatment group.

Table 4. Sample Size and Exact 90% CI for ORR in each treatment group

N per treatment group	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

5.1.2. Decision rules

Phase 1b lead-in

The Table 5 below 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, there is a greater than 97% probability of confirming safety and escalating to avelumab 1200 mg Q3W. Conversely, for a DLT that occurs with a rate of 60%, the probability of escalating is 5%.

Table 5. Probability of Escalating Dose Level of Avelumab to 1200 mg Q3W after Phase 1b Lead-in of Each Cohort (from A1 to A3 and from A2 to A4)

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.

Phase 2

There are no formal decision rules in this phase of the study.

5.2. General Methods

As described in Section 3.4, in this study '**treatment group**' refers to one of the following:

- 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 chemotherapy doublet will be administered IV as shown in Table 6.

Table 6. Chemotherapy Doublets (IV)

Chemotherapy Doublet	Dose(s) and Schedule (21-day cycle)[a]	Cohort	Tumor Type
Pemetrexed/Carboplatin		A1, A3	Non-squamous NSCLC
Pemetrexed	500 mg/m^2, Day 1		
Carboplatin	AUC 5, Day 1		
Gemcitabine/Cisplatin		A2, A4	UC
Gemcitabine	1000 mg/m^2, Day 1 and Day 8		
Cisplatin	70 mg/m^2, Day 1		

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

Baseline characteristics, disposition and efficacy data will be summarized based on the FAS by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

DLTs will be summarized based on the DLT-evaluable set by treatment group including data from Phase 1b lead-in only.

Other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the safety analysis set by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

PK data will be summarized based on the PK analysis sets by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

Biomarker data will be summarized based on the biomarker analysis sets by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

Immunogenicity data will be summarized based on the immunogenicity analysis set by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The ‘center’ factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.2.8 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'On-Study Cancer Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.2.8 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'On-Study Cancer Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits (if such analyses are performed).

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the first dose of study treatment.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist. If this is performed, a footnote or other documentation in the clinical study report (CSR) detailing the exclusions will be provided.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined at the discretion of the clinical pharmacologist. If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables or flagged in the listings and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.

- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

Imputation rules for date of last contact and efficacy assessments

5.3.2.5. Date of last contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (eg. blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact where “Subject Remains in Follow-up” or “Subject No Longer Being Followed for Survival” collected on the “Survival Follow-up” eCRF
- Study drug start and end dates
- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.2.6. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact

- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.2.7. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.2.8. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment. If the imputation results in an end date prior to the imputed start date then the imputed start date should be set to the end date.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.

- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary analysis

The following analyses will be based on the DLT-evaluable set for patients in the Phase 1b lead-in. DLTs will be listed and summarized by treatment group.

6.1.2. Objective response as assessed by the Investigator per RECIST v1.1

6.1.2.1. Primary analysis

The following analyses will be based on the FAS by treatment group using the data from the combined Phase 1b lead-in and Phase 2. Assessment of response will be made using RECIST v1.1. Assessments below refer to investigator assessment.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)

- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment group will also be calculated along with the 2-sided 95% CI using the Clopper-Pearson method [2] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

In addition, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), PD, and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)

- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (ie, SD of insufficient duration).

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 1.1.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS by treatment group using the data from the combined Phase 1b lead-in and Phase 2. Assessment of response will be made using RECIST v1.1. Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameters of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Duration of response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 7.

$$\text{DR (months)} = [\text{date of event or censoring} - \text{first date of OR} + 1]/30.4375$$

Table 7. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 12 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given prior to PD or death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 3, 6, 9, 12 months and every 6 months after as appropriate will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 8 following the hierarchy shown.

Table 8. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy before event	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of first dose of study treatment]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

6.2.2.3. Time to response

Time to response (TTR) is defined, for patients with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – date of first dose of study treatment +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.4. Progression-free survival

Progression-Free Survival (PFS) is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment 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 (ie ≤ 12 weeks after the date of first dose of study treatment) in which case the death will be considered an event.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 6 weeks until PD regardless of initiation of subsequent anti-cancer therapy. After 8 time (one year) from the date of first dose of study treatment, tumor assessments will be conducted less frequently, ie, at 12-week intervals.

The censoring and event date options to be considered for the PFS analysis are presented in Table 9.

PFS (months) = [date of event or censoring– date of first dose of study treatment +1]/30.4375

Table 9. Outcome and Event Dates for PFS Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	date of first dose of study treatment [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤12 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given prior to PD or death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤12 weeks after the date of first dose of study treatment and did not initiate new anti-cancer therapy, the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rates at 3, 6, 9, 12, 15 months and every 6 months after as appropriate will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The

estimate of the standard error will be computed using Greenwood's formula. PFS will be displayed graphically and analyzed using Kaplan-Meier methodology.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for PFS

A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators, including the median time of follow-up for PFS with 2-sided 95% CIs.

6.2.2.5. Overall Survival

Overall survival (OS) is defined as the time from the date of first dose of study treatment to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 3, 6, 9, 12, 15, 18 months and every 6 months after as appropriate will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival

function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[3] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula. OS will be displayed graphically and analyzed using Kaplan-Meier methodology.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 11 following the hierarchy shown.

Table 11. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ date of first dose of study treatment]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 14 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators, including the median time of follow-up for OS with 2-sided 95% CIs.

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group.

C_{max} and C_{trough} for avelumab, and C_{max}, C_{trough}, T_{max}, and $AUC_{ss,\tau}$, as data permit for each chemotherapy agent, will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, cycle, and day (as applicable).

Dose normalized parameters (eg, $C_{max}(dn)$, $C_{trough}(dn)$) will be reported as appropriate.

Pharmacokinetic parameters for avelumab and each chemotherapy (carboplatin, cisplatin, gemcitabine, pemetrexed) will be taken from observed values or derived from plasma concentration-time data as described in Section 3.2.2.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations will be presented in tabular form by treatment group, dose level, cycle, day and nominal time. Additionally, similar descriptive statistics may also be generated for dose-normalized avelumab pharmacokinetic parameters.

- Linear-linear and/or log-linear plots of mean, median and/or individual plasma concentrations by nominal time for chemotherapy (carboplatin, cisplatin, gemcitabine, pemetrexed), including individual bioanalytically-quantified analytes associated with each study drug as applicable, may be presented for PK sampling days by treatment group, cycle, and study day. Patients who have undergone intrapatient dose reduction or escalation will be excluded from the median plasma concentration-time plots.

- Pharmacokinetic parameters for avelumab and each chemotherapy (carboplatin, cisplatin, gemcitabine, pemetrexed) will be listed and summarized by treatment group/dose level, cycle and study day (as applicable) using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). For T_{max}, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. If an intrapatient dose escalation or reduction occurs, dose-dependent PK parameters (AUC, C_{max} and $C_{trough,}$ as applicable) for that patient may be dose-normalized when it is known that the drug exhibits linear PK within the dose range and other PK parameters will be reported as estimated; or may only be included in descriptive statistics and summary plots up to the time of the dose change. In addition, dose-normalized C_{max} and C_{trough} parameters for avelumab will be summarized (as described above) using data pooled across treatment groups in which different avelumab doses were administered.

- Box plots for selected PK parameters (ie. C_{max} and/or C_{trough} for avelumab) will be generated for each treatment group. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing the PK parameter for each drug in individual patients will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots. In addition, box plots for dose-normalized avelumab C_{max} and C_{trough} parameters will be created using either data pooled across treatment groups in which different avelumab doses were administered (if needed to increase sample size in summary figures) or separated by treatment group (to illustrate dose linearity considerations).

- C_{trough} for avelumab will be plotted for each treatment group using a box-whisker plot by cycle and day within cycle in order to assess the attainment of steady-state.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any

association between avelumab and chemotherapy (carboplatin, cisplatin, gemcitabine, pemetrexed) exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

Secondary endpoints in the study are candidate predictive biomarkers in tumor tissue including PD-L1 expression and mutational load at baseline and change in PD-L1 expression upon treatment.

Biomarker data will be analyzed based on the full analysis sets as defined in Section 4.3.3. Data will be presented by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

Biomarkers will be listed and summarized at all timepoints described below:

- Tumor based biomarkers from archival FFPE tumor tissue block at screening
- Tumor based biomarkers from de novo tumor biopsy at screening, on treatment and end of treatment.

Where patients provide both archival and de novo samples at screening, data from the de novo sample will be used in the summary analysis.

For both biomarkers, patients may be classified as positive, negative, unknown, or some other category according to scoring algorithms and cut-offs established from external sources. If no external standards exist, biomarkers may be stratified using the median, quartiles and tertiles. The number and percentage of patients in each category will be tabulated.

BOR and OR will be summarized by treatment group and for each category following the methodology outlined in Section 6.1.2.1. Tumor shrinkage will be plotted by treatment group and by biomarker category following the methodology outlined in 6.2.2.1.

DR and PFS (if meaningful) will be summarized for the cohort of UC patients that is expanded to Phase 2 (A2 or A4) for each biomarker category following the methodology outlined in Sections 6.2.2.2 and 6.2.2.4. The censoring rules for DR and PFS are as described in Table 7 and Table 9.

6.2.6. Endpoints for immunogenicity data of avelumab

ADA and Nab data will be listed and summarized for avelumab by treatment group including data from the combined Phase 1b lead-in and Phase 2.

The percentage of patients with positive ADA and neutralizing antibodies each will be summarized. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. A comparison of the safety, efficacy, and avelumab PK endpoints between avelumab ADA and nAb positive vs. negative patients may be performed, if data permit.

Blood samples for avelumab immunogenicity testing will be collected from all patient's pre-dose on Day 1 of Cycles 1, 2, 3, 6, 10, and 14, and at End of Treatment.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb. Analyses of nAb data described in the following sections will be conducted contingent upon assay and data availability at the time of reporting.

Patients will be characterized into different ADA categories based on the criteria defined in Table 12.

Table 12. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative patients (titer < cutpoint)	Number of patients with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive patients (titer ≥ cutpoint)	Number of patients with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of patients with valid baseline ADA result
Treatment-boosted ADA*	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab	Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response*	If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response*	If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable. * ADA category may be reported if necessary.

Patients will be characterized into different nAb categories based on the criteria in Table 13. For nAb, treatment-boosted is not applicable since no titer result is available.

Table 13. Patients Characterized Based on Neutralizing Antibody Results (nAb Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
nAb never-positive	No positive nAb results at any time point (including no positive ADA results at any time point and no nAb results)	Number of patients with at least one valid ADA result at any time point
nAb ever-positive	At least one positive nAb result at any time point	Number of patients with at least one valid ADA result at any time point
Baseline nAb positive	A positive nAb result at baseline	Number of patients with valid baseline ADA result
Treatment-induced nAb	Patient is not nAb positive at baseline and has at least one positive post-baseline nAb result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)
Transient nAb response*	If patients with treatment-induced nAb have (a single positive nAb result or duration between first and last positive result <16 weeks) and nAb result at the last assessment is not positive.	Number of patients with at least one ADA valid post-baseline result and without positive baseline nAb result (including missing, NR)
Persistent nAb response*	If patients with treatment-induced nAb have duration between first and last positive nAb result ≥16 weeks or a positive nAb result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)

ADA = antidrug antibody, nAb = neutralizing antibody, NR = not reportable. * May be reported if necessary.

The number and percentage of patients in each ADA and nAb category (as appropriate) will be summarized.

In order to derive and interpret persistent and transient ADA responses, the ADA and nAb analyses described below will include patients with treatment-induced ADA or nAb, respectively.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND patient is ongoing treatment with avelumab, or
- the last ADA assessment is positive AND patient discontinued treatment with avelumab AND the last planned ADA assessment (end of treatment) is after the cut-off date.

Time to nAb response and duration of nAb response are defined similarly based on first and last positive nAb result.

Based on the results observed, additional analyses may be performed for ADA including PK, safety and/or efficacy relationships.

6.4. Subset Analyses

ORR for the UC patients (Cohort A2 and A4) including the data from the combined Phase 1b lead-in and Phase 2 in the following subsets: patients with visceral disease (Yes, No). Subset analyses will be performed only if there are at least 10 patients in the associated cohorts and each subset.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS separately by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

6.5.1.1. Demographic characteristics

Demographic characteristics will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - Age (years): summary statistics

- Age categories:
  - < 65 years, ≥ 65 years
  - < 65, 65-<75, 75-<85, ≥ 85 years
- Pooled Geographical Region (as applicable):
  - North America
  - Europe
  - Asia
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall treated population)
- Geographic Region (as applicable):
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis' and RECIST eCRF pages will be summarized by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to date of first dose of study treatment (months), defined as (date of first dose of study treatment – date of initial diagnosis)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No)
- Involved tumor sites at baseline

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' eCRF page) and derived variables as above.

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Anti-Cancer Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer therapy
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 0, 1, 2, 3, ≥4
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic, Local regional Disease-Recurrence
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

Prior anti-cancer drug therapies will be included in the listing that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

6.5.2. Study conduct and patient disposition

The following analyses will be performed based on the FAS separately by treatment group including the data from the combined Phase 1b lead-in and Phase 2.

6.5.2.1. Patient disposition

The percentages below will be calculated based on the number of patients in the FAS in each treatment group.

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated patients in each of the analysis sets defined in Section 4
- Number and percentage of patients with study drug ongoing (separately for each study drug administered in combination)
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation
- Number and percentage of patients who entered long-term follow-up
- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated patients by center

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of the study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn

- Patients who receive the wrong treatment
- Patients who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set by treatment group.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + 21 – 1 day.

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (infusion cyclical). The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided for the following:

- Avelumab administered as a 1-hour IV infusion at a fixed dose of 800 mg once every 3 weeks in 3-week cycles.

- Pemetrexed administered as a 10-minute IV infusion at a dose of 500 mg/m^2 once every 3 weeks in 3-week cycles

- Carboplatin administered as a 60-minute IV infusion at a dose of AUC 5 mg/mL/min once every 3 weeks in 3-week cycles

- Gemcitabine administered as a 30-minute IV infusion at a dose of 1000 mg/m^2 at Day 1 and Day 8 in 3-week cycles

- Cisplatin administered as a 60-minute IV infusion at a dose of 70 mg/m^2 once every 3 weeks in 3-week cycles

Note: The Intended Cumulative Dose and the Intended DI remain constant for all cycles; the intended dose level is fixed at the start of treatment and the intended treatment cycle duration is the same for the entire dosing period, including the last cycle.

6.5.3.1. Exposure to Avelumab

The dose level for avelumab is calculated as actual dose administered (mg).

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 21 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab – first dose date of avelumab + 21)/7

Cumulative dose (mg) is the sum of the actual doses of avelumab received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/3-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with avelumab (weeks)/3].

Relative Dose Intensity (RDI)

- Intended DI (mg/3-week cycle)
  = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle]
  = [800 (mg)] / [1 (3-week cycle)]
  = 800 (mg/3-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [800 (mg/3-week cycle)]

6.5.3.2. Exposure to Pemetrexed

The dose level for pemetrexed is calculated as actual dose administered/m^2 (mg/m^2). The BSA (m^2) is calculated based on the weight and the height (Section 5.2.8). The last available weight of the patient within 3 days pre-dose Day 1 of each cycle will be used.

Intended duration of treatment with pemetrexed (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 21 – 1

Duration of exposure to pemetrexed (weeks) =

(last dose date of pemetrexed – first dose date of pemetrexed + 21)/7

Cumulative dose (mg/m^2) is the sum of the actual doses of pemetrexed received on study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/m^2/3-week cycle) = [overall cumulative dose (mg/m^2)] / [intended duration of treatment with pemetrexed (weeks)/3].

Relative Dose Intensity (RDI)

- Intended DI (mg/m^2/3-week cycle) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = [500 (mg/m^2)] / [1 (3-week cycle)]
  = 500 (mg/m^2/3-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [500 (mg/m^2/3-week cycle)]

6.5.3.3. Exposure to Carboplatin

The dose level for carboplatin is calculated as actual dose administered AUC (AUC mg/mL/min). Carboplatin dose is calculated based on the Calvert formula.

Intended duration of treatment with carboplatin (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 21 – 1

Duration of exposure to carboplatin (weeks) =

(last dose date of carboplatin – first dose date of carboplatin + 21)/7

Cumulative dose (AUC) is the sum of the actual doses of carboplatin received.

Actual Dose Intensity (DI)

- Overall actual DI (AUC/3-week cycle) = [overall cumulative dose (AUC)] / [intended duration of treatment with carboplatin (weeks)/3].

Relative Dose Intensity (RDI)

- Intended DI (AUC/3-week cycle) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = [5 AUC] / [1 (3-week cycle)]
  = 5 AUC/3-week cycle
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI (AUC/3-week cycle)] / [5 AUC /3-week cycle]

6.5.3.4. Exposure to Gemcitabine

The dose level for gemcitabine is calculated as actual dose administered/m^2 (mg/m^2). The BSA (m^2) is calculated based on the weight and the height (Section 5.2.8). The last available weight of the patient within 3 days pre-dose Day 1 of each cycle will be used.

Intended duration of treatment with gemcitabine (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 21 – 1

Duration of exposure to gemcitabine (weeks) =

(last dose date of gemcitabine – first dose date of gemcitabine + n)/7

with n = 7 if the last dose is at Day 1 of the cycle, and n=14 if the last dose is at Day 8 of the cycle.

Cumulative dose (mg/m^2) is the sum of the actual doses of gemcitabine received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/m^2/3-week cycle) = [overall cumulative dose (mg/m^2)] / [intended duration of treatment with gemcitabine (weeks)/3].

Relative Dose Intensity (RDI)

- Intended DI (mg/m^2/3-week cycle) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = [2 × 1000 (mg/m^2)] / [1 (3-week cycle)] = 2000 (mg/m^2/3-week cycle)

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [2 × 1000 (mg/m^2/3-week cycle)]

6.5.3.5. Exposure to Cisplatin

The dose level for cisplatin is calculated as actual dose administered/ m^2 (mg/m^2). The BSA (m^2) is calculated based on the weight and the height (Section 5.2.8). The last available weight of the patient within 3 days pre-dose Day 1 of each cycle will be used.

Intended duration of treatment with Cisplatin (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 21 – 1

Duration of exposure to Cisplatin (weeks) =

(last dose date of cisplatin – first dose date of cisplatin + 21)/7

Cumulative dose (mg/m^2) is the sum of the actual doses of cisplatin received.

Actual Dose Intensity (DI)

- Overall actual DI (*mg/m^2/3-week cycle*) = [overall cumulative dose (mg/m^2)] / [intended duration of treatment with cisplatin (weeks)/3].

Relative Dose Intensity (RDI)

- Intended DI (*mg/m^2/3-week cycle*) = [intended cumulative dose per cycle] / [intended number of 3-weeks in a cycle] = [70 (mg/m^2)] / [1 (3-week cycle)] = 70 (mg/m^2/3-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI] = 100 × [overall actual DI] / [70 (mg/m^2/3-week cycle)]

6.5.3.6. Dose reductions

Applicable to avelumab, carboplatin, cisplatin, gemcitabine and pemetrexed. Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.3.7. Dose delays

Applicable to avelumab, carboplatin, cisplatin, gemcitabine and pemetrexed.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

Dose Delay for Dose x (days) = Date of Dose x – Date of Dose (x-1) – Planned days between two consecutive doses.

Avelumab, carboplatin, cisplatin and pemetrexed

For Cycle 1:

Dose Delay (days) = day of the first day of study drug -1

After Cycle 1:

Dose Delay (days) = Date of dose x of study drug – Date of dose (x-1) of study drug – 21

Gemcitabine

For the first dose of Cycle 1:

Dose Delay (days) = day of the first dose of gemcitabine -1

After the first dose of Cycle 1:

Dose Delay (days) = Date of dose x – Date of dose (x–1) – d,

where d = 7 if Dose x and Dose (x–1) belong to the same cycle, and d = 14 if Dose x is the first dose of a cycle and Dose (x–1) is the last dose of the previous cycle.

Dose delays will be grouped into the following categories:

- No delay
- 1-2 days delay
- 3-6 days delay
- 7 or more days delay

For example, for avelumab, administered on a 3-week schedule, if one patient receives avelumab on Day 1, then the next avelumab administration date will be on Day 22; however, if the patient receives avelumab at Day 23 or 24, this is considered as 1-2 days delay.

No delay and 1-2 days delay will also be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, the worst case of delay if patients have multiple dose delays will be summarized.

6.5.3.8. Infusion rate reductions

Applicable to avelumab.

The number and percentage of patients with at least one infusion rate reduction of ≥50% compared to the first infusion rate reported in the eCRF as well as the frequency of patients with 1, 2, 3 or ≥4 infusion rate reductions of ≥50% will be summarized.

6.5.3.9. Infusion interruptions

Applicable to avelumab, carboplatin, cisplatin, gemcitabine, and pemetrexed.

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (ie, for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set by treatment group.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study drugs and pre-medications for study drug, which are started before the first dose of study treatment.

Concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page.

Summary of concomitant medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

6.5.5. Subsequent anti-cancer therapies

The following analyses will be based on the FAS by treatment group.

Anti-cancer drug treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy' eCRF page.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group.

6.6.1. Adverse events

TEAEs are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described in what follows will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current study data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in 0 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current study data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency based on the frequencies observed for each treatment group.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA PT as event category and MedDRA SOC body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of carboplatin
  - TEAEs leading to dose reduction of cisplatin
  - TEAEs leading to dose reduction of gemcitabine
  - TEAEs leading to dose reduction of pemetrexed
  - TEAEs leading to interruption of avelumab
  - TEAEs leading to interruption of carboplatin
  - TEAEs leading to interruption of cisplatin
  - TEAEs leading to interruption of gemcitabine
  - TEAEs leading to interruption of pemetrexed
  - TEAEs leading to discontinuation of avelumab
  - TEAEs leading to discontinuation of carboplatin
  - TEAEs leading to discontinuation of cisplatin
  - TEAEs leading to discontinuation of gemcitabine
  - TEAEs leading to discontinuation of pemetrexed
  - TEAEs leading to discontinuation of any study drug
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death

  - irAEs
  - IRRs
- TEAEs by SOC and PT and worst grade
- TEAEs related to any drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to dose reduction of each study drug by treatment group:

- TEAEs leading to dose reduction of avelumab by SOC and PT
- TEAEs leading to dose reduction of carboplatin by SOC and PT
- TEAEs leading to dose reduction of cisplatin by SOC and PT
- TEAEs leading to dose reduction of gemcitabine by SOC and PT
- TEAEs leading to dose reduction of pemetrexed by SOC and PT

6.6.1.3. Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.7). These IRRs will be considered as IRRs leading to interruption of infusion.
- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.7).

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of avelumab by SOC and PT
- TEAEs leading to interruption of carboplatin by SOC and PT
- TEAEs leading to interruption of cisplatin by SOC and PT

- TEAEs leading to interruption of gemcitabine by SOC and PT
- TEAEs leading to interruption of pemetrexed by SOC and PT

6.6.1.4. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of carboplatin by SOC and PT
- TEAEs leading to discontinuation of cisplatin by SOC and PT
- TEAEs leading to discontinuation of gemcitabine by SOC and PT
- TEAEs leading to discontinuation of pemetrexed by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity
  - AE not related to study treatment
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs, by treatment group:

- irAEs by Cluster and PT and Maximum CTCAE Grade
- irAEs leading to discontinuation of any study drug, by Cluster and PT
- Serious irAEs, by Cluster and PT.

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of patients with each of the following will be presented for IRRs, by treatment group:

- IRRs by PT and Maximum CTCAE Grade
- IRRs leading to discontinuation of any study drug, by PT
- Serious IRRs, by PT.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria v4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v4.03 will be described using the worst grade. For those parameters which are graded with two toxicities, the toxicities will be summarized separately. Low direction toxicity grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN

- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) will be provided.

Parameters with NCI-CTCAE grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of patients with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE.

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

6.6.6. Vital signs

Weight for the purposes of 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. Height will be measured at screening only.

6.6.7. Electrocardiogram

QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF) and HR using individual (non-averaged) baseline assessments
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms

- HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
- HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
- PR ≥ 220 ms and increase from baseline ≥ 20 ms
- QRS ≥ 120 ms

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

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9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 14. Unless otherwise noted, this case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

Table 14. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list, then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	Steps 3 and 4 will be checked concurrently. Step 5 will be checked if the criteria in Step 4 is met, irrespective of whether the Criteria in Step 3 is met.
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology) B) Histopathology / biopsy consistent with immune-mediated event Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	A) From the AE eCRF page. Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify. B) From the AE eCRF page. B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR, the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 15 and will be identified for IV drugs only.

Table 15. Case Definition for IRRs – IV Study Drugs Administered in Combination (eg, Doublets or Triplets)

Condition	Selection criterion
IRR can be associated with the first IV drug and/or subsequent IV drugs that are administered in combination. Without loss of generality assume triplet IV with D_1 administered first then D_2 then D_3. The IV study drug or drugs associated with the IRR need to be identified in the analysis data set to enable subsequent analysis. The following are not sequential and an AE can be classified as an IRR associated with multiple D_J from one or more of I, II, III, IV, V below: I - If the AE meets [1 AND 2A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 2A1 criterion II - If the AE meets [1 AND 2A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 2A2 criterion III - If the AE meets [3 AND 4B] for any D_J then the AE is classified as an IRR associated with all D_J that meet the 4B criterion. IV- If the AE meets [3 AND 4A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 4A1 criterion V- If the AE meets [3 AND 4A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 4A2 criterion	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}] AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
2A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}]
4A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER')
4B	AE onset on the day after infusion of study drug D_J

Appendix 3. Abbreviations and Definitions of Terms

The following is a list of abbreviations that may be used in the Statistical Analysis Plan.

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BOR	Best Overall Response
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{trough}	Lowest (trough) Concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLT	Dose-Limiting Toxicity
DR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
irAE	Immune-Related Adverse Event
IRR	Infusion related reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
nAb	Neutralizing Antibody
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PR	Partial Response
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
TBILI	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Maximum Plasma Concentration

TTR	Time-to-Tumor Response
UC	Urothelial Cancer
ULN	Upper Limit of Normal
WBC	White Blood Cell