JAVELIN OVARIAN 100

A RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AVELUMAB (MSB0010718C) IN COMBINATION WITH AND/OR FOLLOWING CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED EPITHELIAL OVARIAN CANCER

STATISTICAL ANALYSIS PLAN – B9991010

Compounds:	MSB0010718C
Compound Name:	Avelumab
Version:	V2
Date:	16-Mar-2018

[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991010 is based on the protocol amendment 01 dated 23-Jun-2016.

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2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991010. 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.

CCI [redacted]

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, PK concentration, anti-drug antibodies (ADA; neutralizing antibody [nAb]), CCI [redacted], and tumor assessment results by Blinded Independent Central Review (BICR)).

The primary analysis will include all data up to a cut-off date which is determined by the number of events (progression-free survival [PFS] by BICR) and minimum follow-up of 12 months after the last patient is randomized. The cut-off date is determined once a data extract (before database lock) is available which indicates that the required number of events for PFS by BICR and minimum follow-up of 12 months is expected to occur by the cut-off date.

Due to data cleaning activities, the final number of events might deviate from the planned number. The data cut-off date will not be adjusted retrospectively in this case.

2.1. Study Objectives

Co-Primary Objectives:

1. To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance (Arm C) is superior to platinum-based chemotherapy alone followed by observation (Arm A) in prolonging PFS in patients with previously untreated epithelial ovarian cancer (EOC).

2. To demonstrate that platinum-based chemotherapy alone followed by avelumab maintenance (Arm B) is superior to platinum-based chemotherapy alone followed by observation (Arm A) in prolonging PFS in patients with previously untreated EOC.

Secondary Objectives

- To compare Arm C and Arm B to Arm A in patients with previously untreated EOC, with respect to overall survival (OS).
- To evaluate the anti-tumor activity in each treatment arm.
- To evaluate the overall safety profile in each treatment arm.
- To evaluate the pharmacokinetics (PK) of paclitaxel and carboplatin alone and in combination with avelumab.

- To evaluate the PK of avelumab alone and in combination with carboplatin-paclitaxel (Arms B and C).
- To evaluate the immunogenicity of avelumab alone and in combination with carboplatin-paclitaxel (Arms B and C).
- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in combination with and/or following carboplatin-paclitaxel in pre-treatment tumor tissue, that may aid in the identification of patient subpopulations most likely to benefit from treatment.
- To evaluate patient reported outcome (PRO) in Arm C and Arm B vs Arm A in patients with previously untreated EOC including the assessment of treatment side effects and disease-related symptoms.

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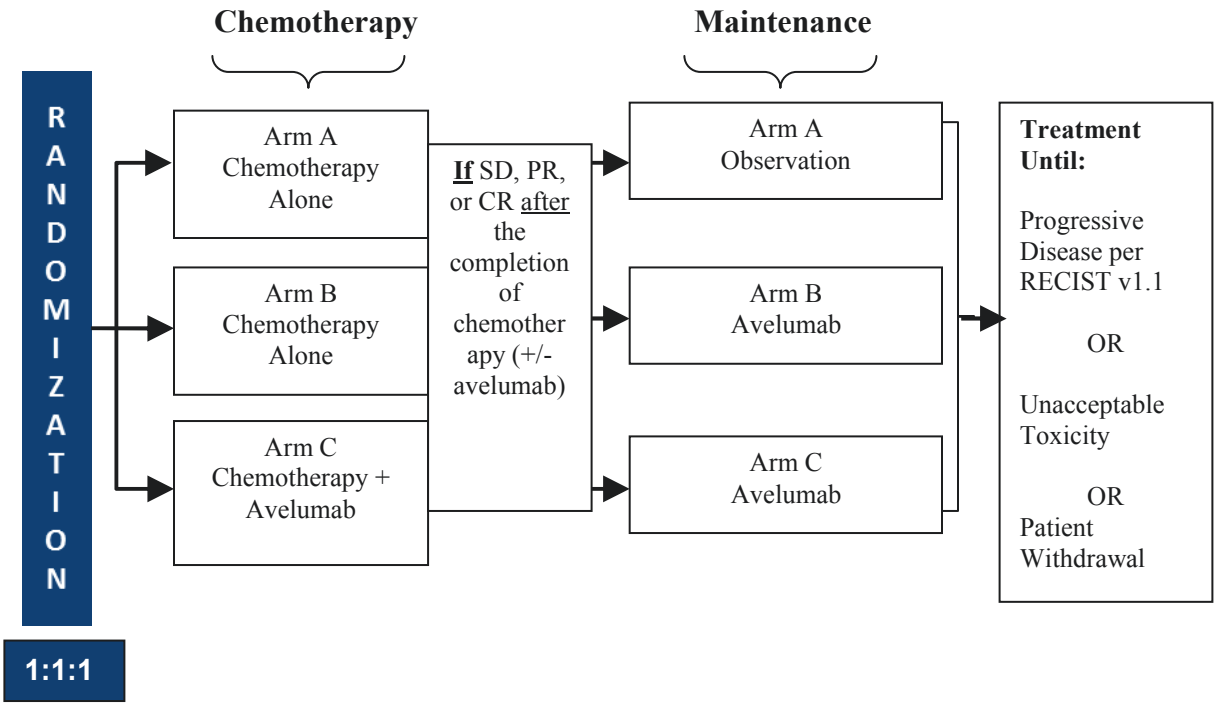
- [redacted]
- [redacted]

2.2. Study Design

This is a Phase 3, open-label, international, multi-center, efficacy, and safety study of avelumab in combination with and/or following platinum-based chemotherapy in adult patients with previously untreated EOC.

The study design is illustrated in the following figure.

Figure 1 Study Design Schema



In this Phase 3 trial, approximately 951 patients who are candidates for frontline platinum-based chemotherapy will be randomized in a 1:1:1 ratio stratified by paclitaxel regimen (every 3 weeks (Q3W) vs weekly (QW)); and by adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection ≤ 1 cm) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant to one of the following treatment arms:

- Arm A: platinum-based chemotherapy alone followed by observation
- Arm B: platinum-based chemotherapy alone followed by avelumab maintenance
- Arm C: avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance.

The assignment to Arm A vs Arm B will be blinded at the time of randomization to patients, investigators, and the Sponsor until completion of chemotherapy.

Crossover between treatment arms will not be permitted.

Intravenous carboplatin-paclitaxel will be used as the chemotherapy backbone, consisting of Q3W carboplatin and the investigator choice of either Q3W or weekly paclitaxel. Once a paclitaxel regimen is chosen for a given patient, it should not be changed for the duration of the study.

Patients may be enrolled either following primary debulking surgery (PDS), or prior to initiation of neoadjuvant chemotherapy. The latter group will undergo interval debulking surgery (IDS) after 3 study cycles of chemotherapy (plus or minus avelumab, depending on

randomization) to be followed by the remainder of chemotherapy (plus or minus avelumab, depending on randomization).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

- PFS as determined by BICR by RECIST v1.1

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

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- Adverse events (AEs) (as graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03); laboratory abnormalities (as graded by NCI CTCAE v4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs)

  AEs will be graded by the investigator according to CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

3.2.2. Efficacy endpoints

- OS; PFS by Investigator assessment as well as Objective response (OR); Duration of response (DR); Maintenance PFS by BICR assessment and Investigator assessment; pathological complete response (pCR); PFS2; and PFS by GCIG criteria.

  OS is defined as the time from the date of randomization to the date of death due to any cause.

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1, from the date of randomization until the date of first documentation of 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.

  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.

  Maintenance PFS is defined, for patients who proceed to the maintenance phase and who do not have PD during the chemotherapy phase, as the time from Cycle 1 Day 1 of the maintenance phase to the date of the first documentation of PD or death due to any cause, whichever occurs first.

  pCR is defined for neoadjuvant patients who undergo IDS as the Chemotherapy Response Score 3 (CSR3) according to Bohm et al, 2015.

PFS2 is defined as time from the date of randomization to the start of second subsequent treatment after first documentation of PD, or death from any cause, whichever occurs first.

PFS by GCIG criteria will be assessed in this study incorporating both RECIST v1.1 and CA-125 (Rustin, G et.al, 2011).

3.2.3. Patient Reported Outcomes

- FOSI-18 and EuroQoL5 Dimension (EQ-5D-5L)

  Patient reported outcomes of HRQoL, ovarian cancer symptoms, treatment side effects, and functioning will be evaluated by FOSI-18 (Jensen 2015) and health status using EuroQol 5 Dimension (EQ-5D-5L) (Herdman 2011; Janssen 2013).

  The FOSI-18 (a revised, more symptom-focused version of the FACT-O) was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system and was specifically created with the input from the Food and Drug Administration (FDA) and validated in ovarian cancer patients. It is specifically designed to be a stand-alone instrument to measure disease symptoms, treatment side effects and function/well-being in patients with ovarian cancer. The FOSI-18 Treatment Side Effect (TSE) subscale uses a set of questions to assess typical bother or side effects associated with cancer medicines, and the Disease Related Symptoms-Physical subscale (FOSI DRS-P), uses a subset of symptoms from the FOSI-18, which are considered to be symptoms specific to ovarian cancer. All FACIT scales are scored so that a high score is good (ie better functioning, or lower symptom burden).

  The EQ-5D-5L is a patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[9] There are 2 components to the EQ-5D-5L, a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.

3.2.4. Pharmacokinetic endpoints

- PK Parameters, including C_{trough}, C_{max}, volume of distribution, (Vd), clearance (CL), area under the concentration time curve (AUC) for avelumab, paclitaxel, and carboplatin, as data permit.

  Dose-normalized parameters (eg, DN-C_{max}, DN-AUC) will be reported as appropriate.

Table 2 PK Parameters to Be Determined for Avelumab

Parameter	Definition	Method of Determination
AUC_{tau}	Area under the plasma concentration-time profile from time zero to the end of the dosing interval (tau)	Linear/Log trapezoidal method
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	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
$t_{½}$ [a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
CL	Clearance	Dose / AUC_{tau} for steady state
Vd	Volume of distribution	Dose / (AUC_{tau} ·kel) for steady state
AUC_{24} (dn)	Dose normalized AUC_{24}	AUC_{24} / Dose
AUC_{last} (dn)	Dose normalized AUC_{last}	AUC_{last} / Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max} / Dose

[a] If data permit

3.2.5. Immunogenicity endpoints

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

3.2.6. Biomarker endpoints

- Candidate predictive biomarkers in tumor tissue including, but not limited to, PD-L1 expression and tumor-infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry (IHC).

Table 3 Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest that are defined by tumor cell morphology and the presence or absence of inflammatory cells	Pathologist, assisted by image analysis
Tumor infiltrating CD8+ lymphocytes	The number of CD8+ cells per unit area and the percent of counted cells that are scored as CD8+	Pathologist, assisted by image analysis

3.3. Exploratory Endpoints

- CCI [redacted]
- CA-125 levels
- CCI [redacted]

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, '**study drug**' refers to avelumab, carboplatin or paclitaxel and '**study treatment**' (or '**treatment arm**') refers to one of the following:

- Arm A = platinum-based chemotherapy alone followed by observation
- Arm B = platinum-based chemotherapy alone followed by avelumab maintenance
- Arm C = avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance.

Start and end dates of study treatment:

The date/time of first dose of study treatment 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 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 and PRO analyses

The last measurement prior to randomization will serve as the baseline measurement for efficacy and PRO analyses. If such a value is missing (since per protocol the first PRO assessment is planned to occur prior to dosing on Cycle 1 Day 1), the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessments data where the baseline assessment would be considered as missing.

Definition of baseline for immunogenicity analyses

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

Definition of baseline for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety 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.

Definition of baseline for biomarker analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for biomarker analyses. For biomarkers that are planned to be measured on Cycle 1 Day 1 (eg, soluble proteins), if the assessment time point is not

collected or is missing, it will be assumed that the measurement was performed prior to first dose of study treatment.

3.4.2. Baseline characteristics

Randomization is stratified by the following, as recorded in the Interactive Response Technology (IRT):

- paclitaxel regimen (Q3W vs QW)
- adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection ≤ 1 cm) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant.

The primary analyses of PFS and OS will be stratified by these randomization stratification factors.

Other baseline characteristics (including demographics, physical measurements, 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 for the first time, or if the worsening of an event is during the on-treatment period.

On-treatment period is defined as follows.

- Arm A:
    - For patients who entered the observation phase, it is the time from the first dose of study treatment through minimum (30 days + the date of end of observation period as reported on the observation end of treatment disposition page, start day of new anti-cancer drug therapy – 1 day).
    - For patients who did not enter the observation phase, it is the time from the first dose of study treatment through minimum (30 days + last dose of study treatment in the chemotherapy phase, start day of new anti-cancer drug therapy – 1 day).
- Arms B and C: 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 Appendices 1 and 2, respectively.

3-Tier Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analyses are generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates these exploratory analyses.

Adverse events and clusters of adverse events, of any causality and treatment-related, will also be summarized following a 3-tier approach. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events or clusters of events of clinical importance and will be described in the Safety Review Plan.

Tier-2 events: These are events that are not Tier-1 but are "common". A MedDRA PT is defined as a Tier-2 event if it is reported by

a) at least 10% of patients with any grade in any treatment arm, or

b) at least 5% of patients with Grade 3, 4 or 5 in any treatment arm.

Tier-3 events: All other AEs that are classified neither as Tier-1 nor Tier-2.

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.

Table 4 summarizes the use of the analysis sets for efficacy, safety, baseline characteristics and exposure.

Table 4 Statistical Analyses by Analysis Set

Endpoints	Full Analysis Set	Per Protocol Analysis Set	Safety Analysis Set
Baseline Characteristics	✓		✓
Prior and Concomitant Therapies	✓		✓
Exposure			✓
Efficacy: Primary	✓	✓	
Efficacy: Secondary	✓	✓ (OS only)	
[redacted]	[redacted]		
Safety			✓

4.1. Full Analysis Set

The full analysis set (FAS) will include all randomized patients. Patients will be classified according to the study treatment assigned at randomization.

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 assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case patients will be classified according to the first study treatment received.

4.3. Other Analysis Set

4.3.1. Per-protocol analysis set

Per-protocol (PP) analysis set is a subset of the FAS and will include patients who do not meet any of the following criteria that could impact the key objectives of the study. Patients who meet any of the following criteria will be excluded from the **PP analysis set for PFS by BICR**.

- Patient did not receive at least one dose of the randomized study treatment
- Patients randomized to Arm A who were treated with avelumab
- Patients randomized to Arms B or C who did not receive at least one dose of avelumab
- Patient without a tumor assessment on or after 3 cycles of chemotherapy (unless PD by BICR or death is observed before that time in which case the patient will not be excluded from the PP analysis set)
- ECOG status ≥ 2 on or prior to randomization date
- Patient does not meet Inclusion Criteria 1, 2 or 3:
    1. Histologically confirmed Stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (according to AJCC/UICC TNM and International Federation of

Gynecology and Obstetrics (FIGO) Staging System 2014 edition), including malignant mixed Müllerian tumors with high grade serous component.

2. Patients must be candidates for platinum based chemotherapy and previously untreated.

3. Patients must have completed a surgical debulking procedure, or be candidates for neoadjuvant chemotherapy.

   a. For patients enrolling after debulking surgery, the following conditions must be met

      - The minimum surgery required is an abdominal surgery with an attempt at cytoreduction providing tissue for histologic evaluation and establishing and documenting the primary site and stage.
      - Patient must be randomized at a maximum of 8 weeks after surgery.

   b. For patients who are candidates for neoadjuvant chemotherapy, the following conditions must be met:

      - A core tissue (not fine needle aspiration) biopsy is required. The tissue must be consistent with a tumor of Müllerian origin.
      - Stage IIIC–IV documented via imaging or surgery (without attempt at cytoreduction).
      - Serum CA-125/ CEA ratio > 25. If the serum CA-125/CEA ratio is < 25, workup should be negative for the presence of a primary gastrointestinal or breast malignancy (< 6 weeks before randomization).
      - Plan to receive carboplatin-paclitaxel neoadjuvant chemotherapy.
      - Randomization must occur within 8 weeks after diagnosis.

Patients who meet any of the following criteria will be excluded from the **PP analysis set for OS**.

- Patient did not receive at least one dose of the randomized study treatment
- Patients randomized to Arm A who were treated with avelumab
- Patients randomized to Arms B or C who did not receive at least one dose of avelumab
- ECOG status ≥ 2 on or prior to randomization date
- Patient does not meet Inclusion Criteria 1, 2 or 3.

4.3.2. PK analysis sets

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

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

4.3.3. Biomarker analysis sets

The biomarker analysis set for biomarkers that are measured only at screening is a subset of the safety analysis set and will include patients who have at least one screening biomarker assessment.

The biomarker analysis set for biomarkers that are measured sequentially is a subset of the safety analysis set and will include patients who have at least one baseline and one on-treatment biomarker assessment for the same marker.

Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

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 in the avelumab containing arms.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

All references to PFS in this section pertain to PFS based on BICR assessment even when not specifically stated.

5.1.1. Hypotheses and sample size determination

The study is designed to test, in parallel, the following hypotheses:

H_{01}: $HR_{PFS(B/A)} \geq 1$, versus H_{a1}: $HR_{PFS(B/A)} < 1$

H_{02}: $HR_{PFS(C/A)} \geq 1$, versus H_{a2}: $HR_{PFS(C/A)} < 1$

where $HR_{PFS\ (B/A\ or\ C/A)}$ represents the hazard ratio (HR) for PFS by BICR assessment in each of the experimental arms vs the control arm.

Approximately 951 patients will be randomized to the treatment arms using a 1:1:1 randomization, stratified by paclitaxel regimen (Q3W vs QW) and by adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection < 1 cm) versus adjuvant (incomplete resection ≥1 cm) vs neoadjuvant.

Overall alpha level for testing hypotheses on the primary endpoint for the 2 treatment comparisons was maintained at 1-sided 0.025 by allocating 0.0125 alpha to each of the comparisons.

Two hundred and seventy-two (272) PFS events by BICR assessment, within each comparison, will be required to have at least 90% power to detect a HR of 0.65 using a 1-sided log-rank test at a significance level of 0.0125, and a 2-look group-sequential design

with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary and a Gamma Family (-5) β-spending function to determine the non-binding futility boundary.

The sample size for this study is determined based on the assumptions that the median PFS in control arm (patients treated with platinum-based chemotherapy alone followed by observation maintenance) is 23 months, (Katsumata et al, 2013) and that treatment with avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance, or treatment with platinum-based chemotherapy alone followed by avelumab maintenance is expected to increase the median PFS to ≥ 35.4 months, corresponding to a HR of 0.65 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each treatment arm, and a non-uniform patient accrual over a 27-month period, and follow-up of approximately 13 months after the last patient is randomized.

The data cut-off for the primary PFS analysis will occur after the target number of events has been reached in both comparisons and the last patient randomized in the study has been followed for at least 12 months after randomization.

The study will also include a formal comparison for OS. The following hypotheses will be tested according to a testing strategy that preserves the overall type I error in the study as described in Section 5.1.2:

H_{03}: $HR_{OS(B/A)} \geq 1$, versus H_{a3}: $HR_{OS(B/A)} < 1$

H_{04}: $HR_{OS(C/A)} \geq 1$, versus H_{a4}: $HR_{OS(C/A)} < 1$

where $HR_{OS\ (B/A\ or\ C/A)}$ represents the HR for OS in each of the experimental arms vs the control arm.

With 376 deaths for each comparison, the study will have 70% cumulative power (unadjusted for the pre-testing, in the hierarchical procedure, of PFS) to detect a HR of 0.75 (80% power to detect a HR of 0.725) using a 1-sided log-rank test at a significance level of 0.0125 and a 5-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary. The sample size for OS is justified based on the assumptions that the median OS in the control arm is 80 months (Katsumata et al, 2013), and that treatment with avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance, or treatment with platinum-based chemotherapy alone followed by avelumab maintenance is expected to increase the median OS to ≥ 106.7 months, corresponding to a HR of 0.75 under the exponential model assumption. The sample size further assumes a 5% drop-out rate for OS in either treatment arm, and a follow-up of approximately 112 months after the last patient is randomized. The data cut-off for the final OS analysis will occur after the target number of events has been reached in both comparisons.

Table 5 summarizes the power to detect several hazard ratios and the estimated duration of the study based on the same number of patients that are planned to be enrolled in the study to meet the primary endpoint and assuming a 5% dropout rate for survival follow-up. These calculations are conditional on achieving statistical significance for the test of PFS.

Table 5 Power to Detect Specific Hazard Ratios for OS

HR under H_{aj}	Power	Calendar time (months) to 376 deaths under H_{aj}
0.75	70%	139
0.73	77 %	140
0. 725	80%	141

Calculations performed using EAST 6.3
j=3, 4

5.1.2. Decision rules

To protect the integrity of the study and to preserve the type I error rate, a fraction of alpha (0.002) for PFS efficacy will be spent at the interim analysis and accounted for in the overall type I error rate if the interim analysis is performed at the planned number of PFS events. The nominal significance levels for the interim and final efficacy analyses of PFS will be determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The overall significance level for the efficacy analysis of PFS, within each comparison, will be preserved at 0.0125 (1-sided test).

Two analyses will be performed for PFS:

1. an interim analysis will be conducted after all patients have been randomized in the study and at least 181 (67%) of the 272 PFS events for each of the comparisons have been documented based on BICR assessment, and
2. the final analysis for PFS will be conducted after all patients randomized in the study have been followed for 12 months and at least 272 PFS events for each of the comparisons have been documented based on BICR assessment.

The interim analyses for PFS will occur at the same time for both treatment comparisons, ie the analysis cut-off date for the test of the 2 hypotheses, $H_{01}$and H_{02}, will be the same and will be set after all patients have been randomized in the study and the target number of events across both treatment comparisons have been reached. If the value of the test statistics for PFS exceeds the associated efficacy boundaries for a comparison, then the experimental treatment associated with that comparison (or treatments if this is met for both comparisons) may be declared statistically significantly superior to the control treatment for PFS. If the value of the test statistics for PFS exceeds the associated futility boundaries, then the experimental treatment associated with that comparison (or the study if this is met for both comparisons) may be stopped for futility.

Table 6 Interim Analysis - Efficacy and Futility Boundaries

	Efficacy boundary		Futility boundary	
	z value	p -value	z value	p -value
PFS Assuming 181 PFS events for each comparison at the time of the IA	< -2.848	p <0.002	z > -0.804	p > 0.211

Since the observed number of events at the interim analysis for each comparison may not be equal to the planned 181 PFS events, the efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions.

If the study continues to final analysis, the p-value that will be used to declare statistical significance at the final analysis will be based on the actual number of PFS events documented at the cut-off date for the final analysis and the α already spent at the interim analysis. Therefore, if the interim analysis occurs after 181 events for each comparison, and the study continues until the final analysis, the observed p-value for the comparison will have to be < 0.012 to declare statistical significance. If the number of events in the final analysis deviates from the expected number of events, the final analysis criterion will be determined so that the overall significance level across all analyses and comparisons is maintained at 1-sided 0.025.

Based on the stopping boundaries defined above and the timing of interim analysis at 67% information fraction the design has the following operating characteristics.

Table 7 Simulated Cumulative Probabilities to Stop for Efficacy or Futility at the Interim or Final PFS Analysis

Scenario	Look	Number of PFS events [a]	Calendar Time (months)	P(Reject H_{0i})	P(Reject H_{ai})
H_{0i} is true (HR=1)	Interim	181	27	0.0018	0.7919
	Final	272	35	0.0137	0.9863
H_{ai} is true (HR=0.65)	Interim	181	30	0.5109	0.0176
	Final	272	40	0.8961	0.1039

Simulations performed in EAST 6.3 with number of simulations = 10,000 and seed= 93480874, 93660830
[a] For each comparison; i=1, 2.

The secondary OS endpoint will be analyzed within each comparison using a hierarchical testing procedure, provided the primary endpoint PFS endpoint is statistically significant favoring the respective experimental arm. An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis will be used so that the 0.0125 overall 1-sided level of significance across all analyses and comparisons is preserved at 0.025. The trial allows for the stopping of the study for a superior OS result, provided the primary PFS endpoint has already been shown to be statistically significant favoring its respective experimental arm.

A maximum of five analyses are planned for OS:

1) an interim analysis at the time of the interim analyses for PFS (provided PFS is significant);

2) an interim analysis at the projected time of the final analysis for PFS (provided PFS is significant);

3) an interim analysis for OS after 188 deaths (50% of the total 376 OS events) have been observed for each comparison;

4) an interim analysis for OS after 282 deaths (75% of the total 376 OS events) have been observed for each comparison;

5) a final analysis for OS after 376 deaths have been observed for each comparison.

The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

If OS is tested alone, independent of the testing strategy for PFS, the design concerning overall survival analyses will have the following operating characteristics. These calculations are unadjusted for the pre-testing of PFS.

Table 8 Simulated Cumulative Probabilities to Stop for Efficacy on Overall Survival at PFS Interim Analysis, Final PFS Analysis, Third and Fourth Interim OS Analyses, or Final OS Analysis

Scenario	Look	Number of deaths	Calendar Time (months)	P(Reject H_{0j})
H_{0j} is true (HR=1)	1st Interim PFS	75	30	<0.0001
	Final PFS	124	40	<0.0001
	50%	188	56	0.0002
	75%	282	84	0.0040
	Final OS	376	121	0.0134
H_{aj} is true (HR=0.75)	1st Interim PFS	68	30	<0.0001
	Final PFS	109	40	0.0009
	50%	188	62	0.0804
	75%	282	94	0.3984
	Final OS	376	138	0.6965

Interim and final PFS analyses calendar time expected at 30 and 40 months, respectively, under H_{ai} (HR for PFS=0.65)

Simulations performed in EAST 6.3 with number of simulations = 10,000 and randomization seed =1131993337, 93862981

i=1, 2; j=3, 4.

5.2. General Methods

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

- Arm A = platinum-based chemotherapy alone followed by observation
- Arm B = platinum-based chemotherapy alone followed by avelumab maintenance

- Arm C = avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance.

Endpoints will be summarized based on the analysis sets described in Table 4 by treatment arm, unless otherwise specified.

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 randomized 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 5.3.3.4 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 6.1.1 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after randomization 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'
- For neoadjuvant patients, ie, patients that answer 'Yes' to the question 'Neoadjuvant patient' in the 'Planned Neoadjuvant Therapy' eCRF page: Surgery date recorded in 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'. For patients that are NOT neoadjuvant: Surgery date recorded in 'Concomitant 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 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant 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 follows.

- Arm A:
    - For patients who entered the observation phase, it is the time from the first dose of study treatment through minimum (30 days + the date of end of observation

period as reported on the observation end of treatment disposition page, start day of new anti-cancer drug therapy – 1 day).

- For patients who did not enter the observation phase, it is time from first dose of study treatment through minimum (30 days + last dose of study treatment in the chemotherapy phase, start day of new anti-cancer drug therapy – 1 day).

- Arms B and C: 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.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2
- BSA (m^2) = ([height (cm) × weight (kg)] / 3600)$^{0.5}$

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.

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 date of randomization.
- For patients with evidence of disease at baseline, 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

For patients who undergo IDS, the IDS date will be identified as follows:

- 'Neoadjuvant Patient' question on 'Planned Neoadjuvant Therapy' eCRF page is answered 'Yes', and
- IDS date is the first surgery date recorded on the 'On-Study Cancer Surgery' eCRF page, where treatment intent is 'Curative Intent' and surgery outcome is 'Resected' or 'Partially Resected'.

For patients who do not undergo IDS, an adequate post-baseline assessment is defined as an assessment with no evidence of disease (for patients with no evidence of disease at baseline) or where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.2.2.4). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

For patients who undergo IDS, since assessments after IDS can only be NE or PD, all post-IDS tumor assessments will be considered adequate. Time points where 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.

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 by the results of interim PK analyses. 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 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

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. 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 (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies (drug, surgery, radiation)
- AE start and end dates
- Last date of contact collected on the 'Survival Follow-up' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date
- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

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.

5.3.3.2. 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

5.3.3.3. 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.

5.3.3.4. 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.

- 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.

5.3.3.5. PRO data

If there are missing items on the FOSI-18, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered, as follows:

Prorated subscale score = [Sum of item scores] × [Number of items in subscale] ÷ [Number of items answered]

When there are missing data, prorating by subscale in this way is acceptable if > 50% of the items were answered. The total score is then calculated as the sum of the un-weighted subscale scores. In addition, a total score should only be calculated if all of the component subscales have valid scores.

For the EQ-5D-5L, questions not answered will be considered missing items and will not be utilized. For EQ-5D-5L, the entire utility score for that cycle is deemed missing if the answer to any one of the 5 dimensions is missing.

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. Progression-free survival as assessed by BICR per RECIST v1.1

6.1.1.1. Primary analysis

The following analyses will be based on the FAS using the strata assigned at randomization. PD below refers to PD by BICR assessment.

Progression-Free Survival (PFS) is defined as the time from the date of randomization 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 randomization unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 18 weeks after the date of randomization) 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, after 3 cycles of chemotherapy, and at the completion of chemotherapy to determine eligibility for maintenance (prior to cycle 1 day 1 of maintenance). For patients who undergo IDS, an additional tumor assessment should be performed after surgery. In the maintenance phase, tumor assessments are performed every 12 weeks until PD regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is 7 days prior to dosing while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration).

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

PFS (months) = [date of event or censoring– date of randomization +1]/30.4375

Table 9 Outcome and Event Dates for PFS and DR Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of randomization[a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 18 weeks after the date of randomization	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	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 ≤18 weeks after the date of randomization, 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 randomization; if the criteria were met the censoring will be on the date of randomization.

The primary efficacy analysis will compare the PFS time based on BICR assessment between each of the experimental arms and the control arm, and will be performed using a 1-sided stratified log-rank test as described in Section 5.1.

The treatment effect, as measured by the hazard ratio, will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata. Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), ie, for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=control arm, 1= experimental arm) and β is the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model (Ties=Discrete option in SAS PROC PHREG).

In order to account for the group sequential design in this study, the repeated CI (RCI) method (Jennison and Turnbull, 2000), will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of PFS.

In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for PFS.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment arm. 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	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR 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 plot will be generated to compare planned and actual relative day of tumor assessments by treatment arm. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment arms reversing the PFS censoring and event

indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median time of follow-up for PFS with 2-sided 95% CIs. In particular, the rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be estimated with corresponding 2-sided 95% CIs.

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS by treatment arm unless otherwise specified. Assessment of response will be made using RECIST v1.1.

Response endpoints will be analyzed separately based on BICR assessments and based on investigator assessment. PFS by investigator assessment will be analyzed as a secondary endpoint using the same methodology that is described in Section 6.1.1.1 now referring to PD by investigator assessment instead of PD by BICR assessment; RCI will not be calculated.

6.2.2.1. Overall survival

The following analyses will be based on the FAS using the strata assigned at randomization.

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

OS (months) = [date of death or censoring– date of randomization +1]/30.4375

The primary analysis of OS will compare the OS time between each of the experimental arms and the control arm, and will be performed using a 1-sided stratified log-rank test as described in Section 5.1.

The treatment effect will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata to calculate the hazard ratio. Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), ie for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=control arm, 1= experimental arm) and β is the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model (Ties=Discrete option in SAS PROC PHREG).

In order to account for the group sequential design in this study, the repeated CI (RCI) method (Jennison and Turnbull, 2000), will be used to construct the 2-sided RCIs for the hazard ratio at the interim and the final analyses of OS.

In addition, the unadjusted 95% CIs for the hazard ratio will also be reported at the interim and the final analyses for OS.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 78, 96, 120 and 144 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment arm. 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 randomization OR End of study (EOS) = Subject refused further follow-up]	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 arms reversing the OS censoring and event indicators. Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median time of follow-up for OS with 2-sided 95% CIs. In particular, the rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 78, 96, 120 and 144 months will be estimated with corresponding 2-sided 95% CIs.

6.2.2.2. Sensitivity analyses for progression-free survival

The following sensitivity analyses will be performed to explore the robustness of the primary analysis results. These analyses are regarded as purely exploratory. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) described in Section 6.1.1.1 with the modifications below:

- PFS based on BICR assessment and counting all PD and deaths as events regardless of missing assessments or timing of the event
- PFS based on BICR assessment on the PP analysis set for PFS
- PFS based on BICR assessment using an unstratified analysis
- PFS based on BICR assessment using strata derived according to eCRF data instead of those entered in IRT
- PFS based on BICR assessment modifying the censoring rules in Table 9 to consider all deaths as events
- PFS based on BICR assessment modifying the censoring rules in Table 9 with initiation of subsequent anti-cancer therapies not used as a censoring reason.

The two stratification factors will be derived as follows based on eCRF data.

- Paclitaxel QW vs Q3W

  The intended dose regimen recorded on the paclitaxel dosing eCRF page on Cycle 1 Day 1 will be used to determine the paclitaxel regimen.

- Adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection ≤1 cm) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant

  If the answer to the question 'Neoadjuvant Patient' is 'Yes' on the 'Planned Neoadjuvant Therapy' eCRF page, the patient will be classified as neoadjuvant. Otherwise the patient will be classified as adjuvant. Note that some neoadjuvant patients may not undergo the planned IDS; this does not impact their classification as neoadjuvant.

  The detailed classification of adjuvant patients by primary debulking surgery result cannot be verified by data collected on the eCRF. If the randomization stratification information entered by the investigator in the IRT is 'adjuvant', then the detailed adjuvant classification as recorded in IRT is used; if the randomization stratification information entered by the investigator in the IRT is 'neoadjuvant', then the protocol deviation data will be used to identify the detailed adjuvant classification.

Methods for evaluating the validity of model assumptions

Schoenfeld residuals for the stratified Cox proportional regression model will be plotted to investigate graphically violations from the proportional hazards (PH) assumption; a non-zero slope is evidence of departure from proportional hazards (PH). The PH assumption will be formally tested using Schoenfeld's residual test (Schoenfeld, 1980; Therneau & Grambsch, 2000). Large departures from PH will be evidenced by a p-value <0.05.

In addition, the PH assumption will be checked visually by plotting

-log(log(S(t)) versus log(t) ,

where S(t) is the estimated survival function (for PFS) at time t.

If these show large departures from proportional hazards, then PFS by BICR assessment will also be analyzed based on restricted mean survival time (RMST) differences (Zhang, 2013).

Restricted Mean Survival Time (RMST)

The hazard ratio estimate from the Cox proportional hazard model is routinely used to empirically quantify the between-arm difference under the assumption that the ratio of the two hazard functions is constant over time. When this assumption is plausible, such a ratio estimate may capture the relative difference between two survival curves. However, the clinical meaning of such a ratio estimate is difficult, if not impossible, to interpret when the underlying PH assumption is violated (ie, the hazard ratio is not constant over time).

The RMST is a robust and clinically interpretable summary measure of the survival time distribution. Unlike median survival time, it is estimable even under heavy censoring. There is a considerable body of methodological research (eg, Royston and Parmar, 2011; Uno,Wei, et al., 2014; Zhang, 2013) about the use of RMST to estimate treatment effects as an alternative to the hazard ratio approach.

The RMST methodology is applicable independently of the PH assumption and can be used, at a minimum, as a sensitivity analysis to explore the robustness of the primary analysis results. However, when large departures from the PH assumption are observed, the log-rank test is underpowered to detect differences between the survival distributions for the treatment arms, and a test of the difference between the RMST for the experimental arm and the control arm may be more appropriate to determine superiority of the experimental arm compared to the control arm with respect to the time-to-event endpoint.

In particular, as it pertains to the **cut-off point (τ)** to evaluate the RMST, it is noted that the cut-off point should not exceed the minimum of the largest observed time for both treatment arms so that the RMST of all treatment arms being evaluated can be adequately estimated and comparison between treatments is feasible; τ should be clinically meaningful and closer to the end of the study follow-up so that the majority of survival outcomes will be covered by the time interval. The RMST up to time τ can then be interpreted as the expected survival time restricted to the common follow-up time τ among all patients. The selection of τ should ensure that the RMST evaluation will not go beyond the maximum time point where the evaluation can be performed while also taking into account a large period of time that is expected to provide a meaningful assessment of treatment effect. To avoid arbitrary selection of the common cut-off τ for both treatment arms, three sets of analyses will be performed:

- τ_1 = minimum of (largest observed survival time for experimental arm, largest observed survival time for control arm).

- τ_2 = minimum of (largest survival event time for experimental arm, largest survival event time for control arm).

- τ_3 = midpoint between τ_1 and τ_2.

In this section, 'survival' is meant to denote PFS.

The treatment effect between each of the experimental arms and the control arm will be assessed based on the difference in RMST. The associated 95% CI for the difference in means and 1-sided p-value will be generated.

BICR vs Investigator assessment

A summary of the BICR assessment versus investigator assessment will be provided including numbers of concordant and discordant assessments as well as the number of cases where PFS event was assessed at different timepoints based on BICR and investigator assessments.

Table 12 outlines the possible outcomes by investigator and BICR (Amit et al. 2011).

Table 12 Possible Outcomes for Investigator vs BICR

		BICR	
		Event	**No Event**
Investigator	**Event**	a = a1 + a2 + a3	b
	No Event	c	d

a1: number of agreements on timing and occurrence of event;
a2: number of times agreement on event but INV declares event later than BICR;
a3: number of times agreement on event but INV declares event earlier than BICR;
N= a+b+c+d.
The timing agreement for event is defined as a window of ± 7 days.

The following measure of discordance will be calculated for each treatment arm:

- Total Event Discrepancy Rate: (b+c) / N
- Early Discrepancy Rate (EDR): (a3+b) / (a+b)
- Late Discrepancy Rate (LDR): (a2+c) / (a2+a3+b+c)
- Overall Discrepancy Rate: (a2+a3+b+c) / N

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares PFS event earlier than BICR within each treatment arm as a proportion of the total number of investigator assessed PFS events.

The LDR quantifies the frequency with which the investigator declares PFS event later than BICR as a proportion of the total number of discrepancies within the treatment arm.

Discordance metrics are calculated for each treatment arm and, for each metric, the difference in discordance between the experimental and control arms is used to evaluate potential bias. If the discordance is similar across the treatment arms then this suggests the absence of evaluation bias favoring a particular treatment arm. A negative differential discordance for EDR and/or a positive differential discordance for LDR may be indicative of investigator evaluation bias in favor of the experimental arm (Amit et al, 2011).

Exploratory analyses to investigate the impact of potential prognostic or effect modifying (predictive) factors

See subgroups as defined in Section 6.4.

Multivariable Cox regression analysis will be carried out to assess and adjust the treatment effect for relevant baseline factors of potential prognostic impact. A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata which will be included in all models during the selection procedure. The Cox's Proportional Hazard model is defined as:

$$h(t) = h(0;t)\, e^{Xb}$$

where h(0;t) defines the baseline hazard function and X defines the vector of explanatory variables and b the unknown vector of regression parameters.

In the stepwise selection procedure, variables are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further variable can be added to the model or if the variable just entered into the model is the only variable removed in the subsequent backward elimination. The level of significance for an explanatory variable to enter the model is set to 0.15 (p-value of Score test) and the significance level for removing it is set to 0.40 (p-value of Wald test). This analysis will be performed using the stepwise selection method in SAS (Proc PHREG). Once this procedure stops, the factor 'treatment arm' will be added to the last selected model in order to evaluate the effect of treatment on PFS time when adjusted for the selected explanatory variables. The hazard ratios of all selected explanatory variables and of treatment effects will be reported including 2-sided 95% CIs. No interactions will be considered. Post-baseline factors will not be considered for the model.

6.2.2.3. Sensitivity analyses for overall survival

The following sensitivity analyses will be performed to explore the robustness of the primary analysis results for OS. These analyses are regarded as purely exploratory. The sensitivity analyses will repeat the primary analysis (p-value, HR and 95% CIs) described in Section 6.2.2.1 with the modifications below:

- PP analysis set;
- unstratified;

- using strata derived according to eCRF data instead of that entered in IRT (as derived in Section 6.2.2.2).

Methods for evaluating the validity of model assumptions

The same methodology described in Section 6.2.2.2 for PFS will be used for OS.

Exploratory analyses to investigate the impact of potential prognostic or effect modifying (predictive) factors

The same methodology described in Section 6.2.2.2 for PFS will be used for OS.

6.2.2.4. Objective response and tumor shrinkage

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of randomization 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.

BOR Based on Confirmed Responses:

- 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 randomization 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 randomization and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of randomization (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-tumor 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 arm will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (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 evidence of disease at baseline
- 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 randomization)
- PD too late (>12 weeks after the date of randomization)

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).

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 arm. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.5. Disease control

Disease Control (DC) is defined as BOR of CR, PR, non-CR/non-PD or SD. DC rate (DCR) is the proportion of patients with DC.

DCR will be summarized by frequency counts and percentages.

6.2.2.6. 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 as described for PFS in Table 9.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rate at 6, 12, 18, 24, and 30 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

6.2.2.7. Maintenance PFS by BICR assessment

Maintenance PFS by BICR is defined, for patients who proceed to maintenance phase and who do not have PD by BICR during the chemotherapy phase, as the time from Cycle 1 Day 1 of the maintenance phase to the date of the first documentation of PD by BICR or death due to any cause, whichever occurs first. Patients who are censored for the PFS analysis by BICR during the chemotherapy phase for reasons other than 'ongoing without an event', are excluded from this analysis.

Maintenance PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after 2 or more missing tumor assessments during the maintenance phase. Patients who do not have an adequate tumor assessment after the initiation of the maintenance phase will be censored on Cycle 1 Day 1 of the maintenance phase, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment in the maintenance phase (ie, ≤ 24 weeks after Cycle 1 Day 1 of the maintenance phase) in which case the death will be considered an event.

The censoring and event date options to be considered for the Maintenance PFS analysis are presented in Table 13.

Maintenance PFS (months) = [date of event or censoring – Cycle 1 Day 1 of the maintenance phase +1]/30.4375

Table 13 Outcome and Event Dates for PFS Maintenance Analysis

Scenario	Date of event/censoring	Outcome
PD or death [a] – After at most one missing or inadequate tumor assessments after initiation of the maintenance phase, OR – ≤ 24 weeks after Cycle 1 Day 1 of the maintenance phase	Date of PD or death	Event
PD or death - after 2 or more missing or inadequate tumor assessments after initiation of the maintenance phase	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 during the maintenance phase 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	Date of last adequate tumor assessment[b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If the patient dies ≤24 weeks after Cycle 1 Day 1 of the maintenance phase the death is an event with date on death date irrespective of initiation of new anti-cancer therapy.

[b] If there are no adequate assessments after the initiation of the maintenance phase prior to PD or death, then the time without adequate assessment should be measured from the date of Cycle 1 Day 1 of the maintenance phase; if the criteria were met the censoring will be on the date of Cycle 1 Day 1 of the maintenance phase.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median Maintenance PFS time with 2-

sided 95% CIs. In particular, the Maintenance PFS rate at 3, 6, 9, 12, 24, 36, 48 and 60 months (from Cycle 1 Day 1 of the maintenance phase) will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to Table 14 following the hierarchy shown.

Table 14 Maintenance PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate tumor assessments after initiation of the maintenance phase /date of Cycle 1 Day 1 of the maintenance phase	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of Cycle 1 Day 1 of the maintenance phase OR End of study (EOS) after initiation of the maintenance phase and reason = Subject refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page after initiation of the maintenance phase	Lost to follow-up
5	No event and [EOS present after initiation of the maintenance phase OR disposition page for any epoch after initiation of the maintenance phase says patient will not continue into any subsequent phase of the study] and no adequate tumor assessment after initiation of the maintenance phase	No adequate tumor assessment after initiation of the maintenance phase
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 tumor assessments after initiation of maintenance phase

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

6.2.2.8. Maintenance PFS by investigator assessment

Maintenance PFS by Investigator is defined, for patients who proceed to maintenance phase and who do not have PD by Investigator assessment during the chemotherapy phase, as the time from Cycle 1 Day 1 of the maintenance phase to the date of the first documentation of PD by investigator or death due to any cause, whichever occurs first. Patients who are censored for the PFS analysis by Investigator during the chemotherapy phase for reasons other than 'ongoing without an event', are excluded from this analysis.

The same analysis described in Section 6.2.2.7 for Maintenance PFS by BICR assessment will be used for Maintenance PFS by Investigator assessment.

6.2.2.9. PFS2

PFS2 is defined as time from the date of randomization to the start of second subsequent treatment after first PD by Investigator assessment, or death from any cause, whichever occurs first.

PFS2 (months) = [date of event or censoring – date of randomization +1]/30.4375

A patient will be considered to have an event if

1) the patient had objective PD on or prior to start of next-line anti-cancer treatment, AND started a second subsequent anti-cancer treatment

   OR

2) the patient died.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median PFS2 time with 2-sided 95% CIs. In particular, the PFS2 rate at 12, 24, 36, 48, 60 and 80 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

The censoring and event date options to be considered for PFS2, each corresponding censoring reason and its hierarchy are presented in Table 15. Frequency (number and percentage) of patients with an event (second subsequent anti-cancer treatment or death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to Table 15 following the hierarchy shown.

Table 15 Outcome, Event Dates, Censoring Reasons and Hierarchy for PFS2 Analyses

Scenario	Date of event/ censoring	Outcome/ Censoring reason/ Censoring hierarchy
(No PD[a]) and (no death)	Date of last adequate tumor assessment[b] documenting no PD	Censored/ No PD/ 1
(No PD[a]) and death	Date of death	Event (Death)
(PD[a] date > NTX1[c] start date) and (no death)	Start date of NTX1[c]	Censored/ Start of new anti-cancer treatment before PD/ 2
(PD[a] date > NTX1[c] start date) and death	Date of death	Event (Death)
(PD[a] date ≤ NTX1[c] start date) and (no death)		
• If NTX2[d] start date is non-missing	Start date of NTX2[d]	Event (Start of second subsequent anti-cancer treatment)
• Else if [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Subject refused further follow-up]	(Withdrawal of consent date) or (EOS visit date where subject refusal of further follow-up is recorded)	Censored/ Withdrawal of consent/ 3
• Else if [lost to follow-up in any disposition page]	Last contact date	Censored/ Lost to follow-up/ 4
• Else if no prior conditions are met	Last contact date	Censored/ Ongoing without PFS2 event/ 5
(PD[a] and no NTX1[c]) and (no death)	Last contact date	Censored/ Ongoing without PFS2 event/ 6
(PD[a] date ≤ NTX1[c] start date) and death		
• If NTX2[d] start date is non-missing	Start date of NTX2[d]	Event (Start of second subsequent anti-cancer treatment)
• Else if the prior condition is not met	Date of death	Event (Death)

[a] PD is the first PD by investigator assessment per RECIST v1.1, without considering any censoring rules.

[b] If there are no adequate post-baseline assessments, then the censoring date is the date of randomization. If patient has initiated next-line anti-cancer treatment, the last adequate post-baseline assessment on or prior to start date of next-line anti-cancer treatment will be considered.

[c] NTX1 is the first new anti-cancer treatment.

[d] NTX2 is the second new anti-cancer treatment.

The PFS2 time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.2.10. PFS by GCIG criteria based on investigator assessment

PFS from the date of randomization by GCIG criteria will be assessed in this study incorporating both RECIST v1.1 and CA-125 (Rustin, G et.al.) (see Appendix 6 of the protocol) based on Investigator assessment.

PFS by GCIG criteria will be censored if both PFS per RECIST v1.1 and PFS per CA-125 are censored, the date of censoring will be the latest of the two censoring dates.

CA-125 data will be censored on the date of the last CA-125 assessment for patients who start new anti-cancer therapy prior to an event, or for patients with an event after 2 or more missing CA-125 assessments. Patients who do not have an adequate baseline CA-125 assessment or who do not have an adequate post-baseline CA-125 assessment will be censored on the day of randomization with a duration of 1 day.

PFS by GCIG criteria (months) = [date of event or censoring – date of randomization +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median PFS by GCIG criteria time with 2-sided 95% CIs. In particular, the PFS by GCIG criteria rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

Frequency (number and percentage) of patients with each event type (PD by Investigator assessment per RECIST v1.1 or PD by CA-125 or death) and censoring reasons will be presented by treatment arm. Reasons for censoring will be summarized according to the hierarchy shown in Table 16.

Table 16 Censoring Reasons and Hierarchy for PFS by GCIG Criteria Based on Investigator Assessment

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment per RECIST v1.1 and no adequate CA-125 baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event by Investigator assessment per RECIST v1.1 after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event per RECIST v1.1 after 2 or more missing assessments [a]
4	Event per CA-125 after 2 or more (ie, > 12 weeks) missing post-baseline assessments	Event per CA-125 after 2 or more missing assessments
5	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Subject refused further follow-up]	Withdrawal of consent
6	No event and lost to follow-up in any disposition page	Lost to follow-up
7	No event and [EOS present OR 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 and no post-baseline CA-125 assessment	No adequate post-baseline tumor assessment and no adequate post-baseline CA-125 assessment
8	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 by GCIG criteria time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.2.11. pCR

pCR is defined for neoadjuvant patients who undergo IDS (see Section 5.2.11) as the Chemotherapy Response Score 3 (CSR3) according to (Bohm et. al., 2015) (see Appendix 5 of the protocol).

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

6.2.3. Pharmacokinetic endpoints

The central laboratory, analytical laboratories (eg, PK, ADA, NAb), and Pfizer clinical assay group (CAG) colleagues will be unblinded. If the need arises for early analysis of the PK data (before database lock and release of the randomization codes for the study), a PK unblinding plan will be developed. A PK analyst, who is not associated with the study team, will conduct the analysis to avoid unblinding of the study team.

The following pharmacokinetic analyses will be based on the PK analyses set by treatment arm as well as by paclitaxel regimen (weekly vs 3-weekly).

C_{trough} and C_{max} for avelumab will be summarized descriptively. Pharmacokinetic parameters for avelumab will be taken from observed plasma concentration-time data as described in Section 3.2.4.

Standard plasma PK parameters for carboplatin (total and free) and paclitaxel will be estimated using non compartmental and/or compartment methods, if needed. Analysis will include C_{max}, T_{max}, AUC_{tau}, $t_{½}$, CL, and Vd as data permit. Dose-normalized parameters (eg, DN-C_{max}, DN-AUC) will be reported as appropriate.

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 arm, dose level (for paclitaxel and carboplatin as needed), cycle, day and nominal time. Additionally similar descriptive statistics will also be generated for dose-normalized avelumab, paclitaxel and carboplatin pharmacokinetic parameters as appropriate.

- Linear-linear and log-linear plots of mean and median plasma concentrations by nominal time for avelumab, paclitaxel and carboplatin (total and free) will be presented for PK sampling days by treatment arm, cycle, and day. Similar plots will be presented for each individual patient concentrations. Patients who have undergone intrapatient dose reduction or escalation will be excluded from the median plasma concentration-time plots.

- Pharmacokinetic parameters for avelumab, paclitaxel and carboplatin (total and free) will be listed and summarized by treatment arm/dose level (for paclitaxel and carboplatin as needed), cycle and day 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 and C_{max}) 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 AUC parameters will be summarized (as described above) using data pooled across treatment arms in which different avelumab, paclitaxel and carboplatin doses were administered.

- Box plots for AUC and C_{max} for paclitaxel and carboplatin (total and free) and C_{max} and C_{trough} for avelumab will be generated. 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 arm has limited evaluable PK data (n<4), matchstick plots showing changes in AUC and C_{max} 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.

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

Assessment of drug-drug interaction

- Effect of Avelumab on paclitaxel and carboplatin Pharmacokinetics:

The effect of avelumab dosing on paclitaxel and carboplatin PK will be evaluated based on overall assessment of the geometric mean ratios and associated 90% CI for C_{max}, AUC_{inf}, and AUC_{tau} of paclitaxel and carboplatin on Day 1 of Cycle 2 in Arm C compared to those on Day 1 of Cycle 2 of Arm A and B.

- Effect of paclitaxel and carboplatin on Avelumab Pharmacokinetics:

The effect of paclitaxel and carboplatin dosing on avelumab PK will be evaluated based on the overall assessment of the geometric mean ratios and associated 90% CI of C_{max} and C_{trough} of Arm C on Day 1 of Cycle 2 of the chemotherapy phase compared to those on Day 1 of the first maintenance cycle of Arms C.

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 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, but not limited to, PD-L1 expression and tumor infiltrating CD8+ T lymphocytes as assessed by immunohistochemistry (IHC).

Biomarker data will be analyzed based on the biomarker analysis sets as defined in Section 4.3.3, by treatment arm.

If a patient has more than one result at a visit for a specific biomarker analyte, then:

- For continuous data, the duplicate results will be averaged, and the average used in the analysis;

- For non-continuous data (eg, identified genes), the study team will select the record appropriate for analysis. A flag will be added to the data sets indicating which record was selected for analysis.

For PD-L1 expression, patients will be classified as positive and negative according to scoring algorithms and cut-offs established from internal or external sources. Patients whose status cannot be determined are not considered to have screening biomarker assessment per the biomarker analysis set definition, and therefore will be excluded.

For CD8+, if at the time of reporting an internal or external standard becomes available, the above mentioned approach for PD-L1 will be used. Otherwise, data will be categorized using quartiles to define CD8+ subgroups.

The following analyses will be performed for each biomarker secondary endpoint.

Biomarker subgroups as defined above will be used to perform subgroup analyses for efficacy endpoints (PFS by BICR assessment, OS) using the methodology outlined in Section 6.4. In addition, the hazard ratio for the biomarker subgroup level comparisons and the unadjusted 95% CIs for the hazard ratio will be reported for each treatment arm.

CCI

CA-125 levels. CCI

6.2.6. Immunogenicity endpoints

All analyses described below are performed by treatment arm containing avelumab (Arm B and Arm C), and for the avelumab-containing treatment arms combined unless otherwise specified.

Blood samples for avelumab immunogenicity testing will be collected pre-dose and within 2 hours before the start of the avelumab infusion. For Arm C during the chemotherapy phase, it is collected on Day 1 of Cycles 1 through 4. For Arms B and C during the maintenance phase, it is collected on Day 1 and Day 15 of Cycles 1 and 2, and thereafter on Day 1 of each subsequent cycle until Cycle 18, at the End of Treatment and at post-treatment safety follow up (30 days).

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb. As of the finalization of this SAP, the nAb assay is not yet available, therefore the analyses of nAb data described in the following sections will only 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 17.

Table 17 Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Subjects 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 past-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.

Patients will be characterized into different nAb categories based on the criteria in Table 18. For nAb, treatment-boosted is not applicable since no titer result is available.

Table 18 Patients Characterized Based on Neutralizing Antibody Results (nAb Status)

Category	Definition	Subjects at Risk (Denominator for Incidence)
nAb never-positive	No positive nAb results at any time point	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 past-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 = no result.

The number and percentage of patients in each ADA and nAb category will be summarized.

6.2.6.1. Time to and Duration of ADA and nAb response

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.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

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 (post-treatment 30-day safety follow-up) 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.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2011) (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.

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

As data permit, the analyses described above will be repeated for patients with treatment-induced nAb.

6.2.6.2. ADA titer

For patients who are ADA ever positive, the maximum observed ADA titer for a patient will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of patients having each discrete maximum titer value will be tabulated. The denominator to calculate the percentages will be the total number of patients in the associated ADA subcategory.

For patients with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

6.2.6.3. Analysis of PK, safety and efficacy by immunogenicity status

The following ADA and nAb status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive
- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive

nAb

- nAb ever-positive versus nAb never-positive
- nAb: treatment-induced nAb versus nAb never-positive or baseline nAb positive

Data listings will include immunogenicity data together with relevant PK, safety and efficacy data.

PK parameters and immunogenicity status

The following analyses will include patients in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoints pertinent to the immunogenicity analyses are C_{trough} and C_{max}.

Blood samples for avelumab PK will be collected within 2 hours prior to and immediately before the end of avelumab infusion (1 hour post start of avelumab infusion). For Arm C in the chemotherapy phase, it is collected on Day 1 of Cycles 1 to 4. For patients receiving weekly paclitaxel only, an additional avelumab sample will be taken on Day 8 and Day 15 of Cycles 1 to 4 prior to the paclitaxel infusion. For Arms B and C in the maintenance phase, it will be collected on Days 1, 15 and 29 of Cycle 1, and thereafter on Day 1 of every subsequent cycle until Cycle 18, at the End of Treatment and at post-treatment safety follow up (30 days).

C_{trough} and C_{max} will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time and ADA status. Linear-linear and log-linear plots of mean and median for C_{trough} and C_{max} over nominal time and by ADA status will be presented.

Among patients with treatment-induced ADA, analyses will be conducted to assess whether C_{trough} and C_{max} have any changes before and after the first positive ADA assessment. To be included in this analysis, patients must have the same PK parameter available both before and after the first positive ADA assessment. Relative PK day will be calculated as:

(PK assessment nominal day) – (first positive ADA assessment nominal day).

Nominal day is the protocol scheduled timing for an assessment. For example, if C_{trough} is collected on Day 1 of Cycle 2 in the chemotherapy phase and the first positive ADA result is observed on Day 1 of Cycle 3 in the chemotherapy phase, then the relative PK day for this C_{trough} is -21. Linear-linear and log-linear plots of mean and median for C_{trough} and C_{max} over relative PK day will be presented.

As data permit, the analyses described above will be repeated for nAb.

Safety and immunogenicity status

The following analyses will include patients in the immunogenicity analysis set.

The frequency (number and percentage) of patients with each of the following will be presented by ADA status.

- TEAEs, by SOC and PT
- TEAEs leading to dose reduction of avelumab, by SOC and PT
- TEAEs leading to discontinuation of avelumab, by SOC and PT
- TEAEs leading to discontinuation of study treatment by SOC and PT
- Grade ≥ 3 TEAEs, by SOC and PT
- SAEs, by SOC and PT
- IRRs, by PT

For patients who had at least one IRR and have treatment-induced ADA, time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later) will be summarized taking into account whether the IRR occurred on or after the first ADA positive assessment or whether the IRR occurred before the first ADA positive assessment.

As data permit, the analyses described above will be repeated for nAb.

Efficacy and immunogenicity status

For the ADA ever-positive patients, a listing will be prepared with patient ID, start and stop of avelumab treatment, date of first positive ADA result, time to ADA response, duration of ADA response, date of last ADA positive result, BOR, DR, PFS time or censoring time and reason for censoring, and OS time or censoring time and reason for censoring. If applicable, date of first positive nAb result, time to nAb response, duration of nAb response, date of last nAb positive result will also be presented. Tumor-related endpoints will be presented based on BICR assessment and based on Investigator assessment.

For the ADA ever-positive patients, the percent change from baseline in target lesions as well as the first occurrence of a new lesion and patient off avelumab treatment will be displayed against time point (weeks) in a line plot. Additional symbols will indicate the first and last ADA positive result and, if applicable, the first and last nAb positive result. Plot will be presented separately based on BICR assessment and based on Investigator assessment.

6.2.7. PRO endpoints

All PRO analysis will be based on FAS and will include all the assessments per schedule of assessment from baseline to the last PRO assessment, unless otherwise specified. For time-to-event and continuous endpoints, an analysis including assessments from baseline up to EOT (not including EOT) will also be conducted.

Patient reported outcomes of HRQoL, ovarian cancer symptoms, treatment side effects, functioning and time to deterioration will be evaluated by FOSI-18 (Jensen 2015) and health status using EuroQol 5 Dimension (EQ-5D-5L) (Herdman 2011; Janssen 2013).

The primary PRO analysis is designed to determine the effect of Arm C or Arm B compared to Arm A on overall HRQoL, based on the FOSI-18 total score over the course of the study from baseline up to EOT (not including EOT).

6.2.7.1. Scoring procedure

The FOSI-18 and EQ-5D-5L will be scored according to their respective validation papers and user's guides (FACIT 2008; EuroQoL Group 2015). For the EQ-5D-5L, the index scores will be calculated using the published weights (tariffs) for the United Kingdom (UK). Specific country weights may be applied for country specific analyses as needed.

6.2.7.2. Instrument completing rates

For each treatment arm and at each time point, the number and percentage of patients who complete the FOSI-18 and EQ-5D-5L will be summarized, as will the reasons for non-completion of these measures. An instrument is considered complete if at least one item was answered by the patient.

6.2.7.3. Descriptive summaries over time

Absolute scores and change from baseline for the total, all subscales and the single item "I am bothered by side effects of treatment" of the FOSI-18, the EQ-5D-5L, and EQ-VAS will be summarized (as described in Section 5.2.3) at each time point by treatment arm. Line charts depicting the means and mean changes from baseline along with SE error bars over time will be provided for each scale by treatment arm.

For the EQ-5D-5L health status, the proportions of patients reported having "none", "slight", "moderate", "severe", or "extreme/unable" problems at each time point will be calculated, by treatment arm.

6.2.7.4. Time-to-event endpoints

Time to treatment bother in the maintenance phase

Time to Treatment Bother (TTB) will be evaluated in the maintenance phase. TTB is comprised of a single question within the TSE subscale, "I am bothered by side effects of treatment". TTB in the maintenance phase is defined, for patients who proceed to the maintenance phase and who do not have PD by BICR during the chemotherapy phase, as the time from Cycle 1 Day 1 of the maintenance phase to the date of first report of a score of ≥ 2 for at least two consecutive assessments on the side effect bother item.

Patients will be censored at the time when they last completed the TSE sub-scale assessment if they have not reported a TTB score of ≥ 2 for at least two consecutive assessments. Additionally patients missing at least 2 consecutive assessments will be censored on the date of the last non-missing assessment.

TTB (months) = [date of event or censoring – Cycle 1 Day 1 of the maintenance phase +1]/30.4375

The analysis will compare the TTB time between each of the experimental arms and the control arm, and will be performed using a 1-sided stratified log-rank.

The treatment effect, as measured by the hazard ratio, will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata. Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), ie, for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=control arm, 1= experimental arm) and β is the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model (Ties=Discrete option in SAS PROC PHREG).

The unadjusted 95% CIs for the hazard ratio will be reported.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median TTB time with 2-sided 95% CIs. In particular, the TTB rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

Time to deterioration of physical disease-related symptoms

The FOSI DRS-P subscale will also be used to determine the Time to Deterioration (TTD) of disease-related symptoms. TTD is defined as the time from the randomization date to the first time the patient's score shows a 3-point or higher decrease in the FOSI DRS-P score.

Patients will be censored at the time when they last completed a sub-scale assessment if they have not deteriorated. Yost & Eton established that a 3-point or a greater difference on a FACT scale of this length (9 items for FOSI DRS-P subscale) constitutes a meaningful difference in disease symptoms (Yost, 2005).

The analysis will compare the TTD time between each of the experimental arms and the control arm, and will be performed using a 1-sided stratified log-rank.

The treatment effect, as measured by the hazard ratio, will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata. Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG), ie, for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=control arm, 1= experimental arm) and β is the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model (Ties=Discrete option in SAS PROC PHREG).

The unadjusted 95% CIs for the hazard ratio will be reported.

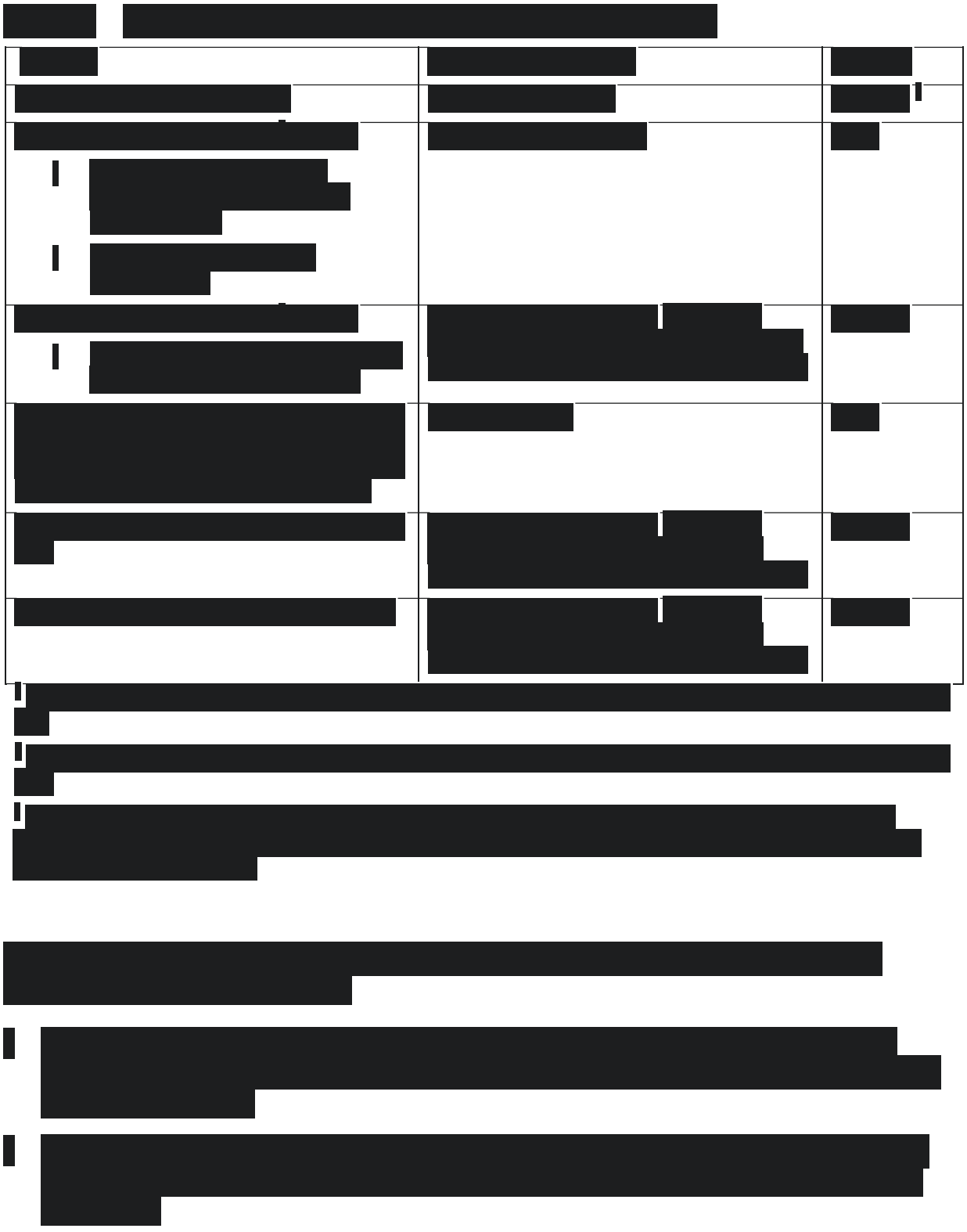
Kaplan-Meier estimates (product-limit estimates) will be presented by treatment arm together with a summary of associated statistics including the median TTD time with 2-sided 95% CIs. In particular, the TTD rate at 9 and 18 weeks and at 8, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley 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 (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.

6.2.7.5. Continuous endpoints

Mixed-effects longitudinal modeling will be carried out for the total, subscale (DRS-P, DRS-E, TSE, FWB) and the single item "treatment bothered" scores of the FOSI-18 and also the EQ-5D-5L and EQ-VAS scores, and will compare each of the experimental arms with the control arm using PROC MIXED. Outcomes are PRO post-baseline scores and the predictors are the corresponding baseline PRO score, treatment, time (treated as a continuous variable), and treatment-by-time interaction. Intercept and time are considered as random effects particular to each subject. All parameter estimates should be obtained using restricted maximum likelihood. The unstructured covariance structure should be used to define covariance between random effects (using option "Type=UN" as a part of the RANDOM statement in PROC MIXED). For the degrees-of-freedom calculations the Kenward and Roger algorithm should be used (using option "ddfm = kr" as a part of the MODEL statement in PROC MIXED). The primary analysis will be applied to all cycles, chemotherapy and maintenance phases, prior to EOT to determine if overall HRQoL, symptoms, treatment side effect, and functioning, have been impacted over the course of the study for the comparisons Arm C vs Arm A and Arm B vs Arm A.

[redacted]

[redacted]



[redacted]

6.4. Subset Analyses

Subset analyses will be performed for PFS per BICR assessment and OS based on the FAS for the subgroups defined below.

[redacted]

The following subgroups will be defined and used for analyses:

- Randomization stratification factors as per IRT
  - paclitaxel regimen (Q3W (Reference) vs QW)
  - adjuvant (complete resection/microscopic disease (Reference)) vs adjuvant (incomplete resection ≤ 1 cm) vs adjuvant (incomplete resection >1 cm) vs neoadjuvant.
- Age
  - Age < 65 years (Reference)
  - Age ≥ 65 years
- Race
  - Caucasian / White (Reference)
  - Asian
  - Black/African American
  - Other
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Latino (Reference)
- Pooled Geographical Region
  - North America
  - Europe (Reference)
  - Asia
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional subgroups if including > 10% of the overall randomized population)
- BRCA 1/2 mutation status
  - Positive (Reference)
  - Negative
  - Unknown
- Stage
  - III (Reference)

- IV

- ECOG Performance Status on or prior to randomization date
  - 0 (Reference)
  - ≥ 1
- CA-125 at baseline
  - ≤2xULN (Reference)
  - >2xULN
- PD-L1 status at baseline
  - Positive (Reference)
  - Negative

  The cut-off will be pre-specified using external data before the analysis.

Subset analyses for PFS and OS will use the primary censoring rules described in Sections 6.1.1.1 and 6.2.2.1. All the subgroup analyses are exploratory. Treatment arms will be compared for PFS and OS using a 2-sided unstratified log rank test for each subgroup level and the unstratified HR and its corresponding 95% CI will be computed per subgroup level.

All the subgroup analyses will be exploratory; no adjustment for multiplicity will be performed. In the case of a low number of patients within a category (<5% of the randomized population), the categories will be pooled.

To assess the heterogeneity of treatment effects for PFS and OS across the subgroup levels, two Cox regression model will be fitted with PFS or OS, respectively, as the dependent variable and subgroup, treatment, and with and without the treatment-by-subgroup interaction as explanatory variables.

- Model 1: factors + treatment + subgroup
- Model 2: factors + treatment + subgroup + treatment × subgroup-variable

A p-value for the interaction test (Likelihood Ratio test) will be provided together with the HR and corresponding 95% CI for the interaction model parameter.

The HR for PFS and OS and corresponding 95% CIs for all subgroups will also be presented in a forest plot.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

The following analyses will be based on the FAS overall and separately by treatment arm.

6.5.1.1. Demographic characteristics

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

- Demographic characteristics
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown
  - Ethnic origin: Hispanic/Latino (Yes/No)
  - 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 randomized 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
- Physical measurements
  - Height (cm)

- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Body Surface Area (BSA) (m^2)

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 arm, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2), BSA (m^2) 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', 'Substance Abuse' and RECIST eCRF pages will be summarized overall and by treatment arm. 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 randomization (months), defined as (date of randomization – date of initial diagnosis)/30.4375
- Time since histopathological diagnosis (months), defined as (date of randomization –date of histopathological diagnosis)/30.4375

Separately from the RECIST eCRF page based on Investigator assessment and based on BICR assessment:

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

From the 'Substance Use' eCRF page:

- Smoking history
  - Never smoker vs current vs former smoker
  - Smoking exposure (pack-years): 0, <20, 20-<40, ≥40 and summary statistics
  - Years since quitting: never smoker, current smoker, <5, 5-<10, ≥10 and summary statistics

  Specifications for computation:

  - Cigarette equivalents are calculated as follows: one cigar is regarded equivalent to 5 cigarettes and 1 pipe is regarded equivalent to 3 cigarettes
  - Duration of nicotine consumption [years]:

    (end of nicotine consumption – start of nicotine consumption + 1) / 365.25
  - Pack-years:
    - calculate cigarette equivalents per day using the conversion factors given above
    - convert to packs per day where 20 cigarettes are regarded as 1 pack
    - pack-years = packs per day × duration of nicotine consumption [years]

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

6.5.1.4. Prior anti-cancer surgery

The prior anti-cancer surgeries are collected under the 'Prior Surgery' eCRF page.

The number and percentage of patients with at least one prior anti-cancer surgery will be tabulated. Treatment intent and surgery outcome will also be summarized.

Prior anti-cancer therapies will be included in the listings that follow with a flag to identify prior therapies.

- Listing of anti-cancer drug therapies
- Listing of anti-cancer radiotherapy
- Listing of anti-cancer surgeries

These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

6.5.2. Study conduct and patient disposition

The following analyses will be performed based on the FAS overall and separately by treatment arm.

6.5.2.1. Patient disposition

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

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to randomization overall and by the main reason for discontinuation
- Number and percentage of randomized patients in each of the analysis sets defined in Section 4
- Number and percentage of randomized patients with study drug ongoing (separately for each study drug when administered in combination)
- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug when 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, a summary of patients who have discontinued all study drugs will be provided.

The results of the randomization algorithm (according to IRT) will be summarized as follows:

- Number and percentage of randomized 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 randomized patients by center
- Number and percentage of randomized patients by randomization strata (IRT)
- Number and percentage of randomized patients by randomization strata (eCRF)
- Cross tabulation: stratum by IRT vs. stratum by eCRF
- Cross tabulation: patients randomized (Arm A/Arm B/Arm C) vs. patients treated (Arm A/Arm B/Arm C/none)

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of a 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 or an incorrect dose
- 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 arm.

All dosing calculations and summaries will be based on 'Parenteral – Drug avelumab' 'Parenteral – Drug paclitaxel', and 'Parenteral – Drug carboplatin' eCRFs pages. A listing of study drug administration will be created with the information collected on the 'Parenteral – Drug avelumab', 'Parenteral – Drug paclitaxel', or 'Parenteral – Drug carboplatin' eCRF pages.

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 days – 1 day if the last cycle occurred in the chemotherapy phase;

- actual cycle end date = actual cycle start date + 42 days – 1 day if the last cycle occurred in the chemotherapy phase

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 (per cycle and overall within a study phase) as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The formulae below should be applied to each study drug separately.

The derivations below are provided for the following.

In the chemotherapy phase

- Avelumab administered as a 1-hour IV infusion at a dose of 10 mg/kg once every 3 weeks in 3-week cycles for 6 cycles
- Paclitaxel QW administered as 80 mg/m^2 IV over 1 hour on Days 1, 8 and 15 of each 3-week cycle for 6 cycles
- Paclitaxel Q3W administered as 175 mg/m^2 IV over 3 hours Day 1 of each 3-week cycle for 6 cycles
- Carboplatin dose AUC 5 or AUC 6 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

In the maintenance phase

- Avelumab administered as a 1-hour IV infusion at a dose of 10 mg/kg once every 2 weeks in 6-week cycles.

Analysis of exposure will be based on the calculated actual dose levels:

- Avelumab - total dose / weight
- Paclitaxel – total dose / m^2
- Carboplatin - AUC.

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

Chemotherapy phase

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 in chemotherapy phase with non-zero dose of study drug + 21 – 1

Duration of exposure to avelumab (weeks) =

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

Cumulative dose in a cycle or overall is the sum of the actual doses of avelumab received in a cycle or overall (in the chemotherapy phase), respectively

Actual Dose Intensity (DI)

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

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/3-week cycle) = 10 (mg/kg/3-week cycle)
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [10 (mg/kg/3-week cycle)]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [10 (mg/kg/3-week cycle)]

Maintenance phase

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of avelumab in maintenance phase +1)/7,

where end date = start date of last cycle in maintenance phase with non-zero dose of avelumab + 42 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab in maintenance phase – first dose date of avelumab in maintenance phase + 14)/7

Cumulative dose in a cycle or overall is the sum of the actual doses of avelumab received in a cycle or overall (in the maintenance phase), respectively

Actual Dose Intensity (DI)

- By cycle actual DI (mg/kg/6-week cycle) = [cumulative dose in the cycle (mg/kg)]/[cycle duration (weeks)/6]
- Overall actual DI (mg/kg/6-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with avelumab (weeks)/6].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/6-week cycle) = 30 (mg/kg/6-week cycle)
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [30 (mg/kg/6-week cycle)]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [30 (mg/kg/6-week cycle)]

6.5.3.2. Exposure to paclitaxel QW

The dose level for paclitaxel QW is calculated as actual dose administered/m^2 (mg/m^2). The actual paclitaxel regimen (QW vs Q3W) is determined using the Cycle 1 Day 1 paclitaxel dose regimen.

Intended duration of treatment with paclitaxel QW (weeks) =

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

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

Duration of exposure to paclitaxel (weeks) =

(last dose date of paclitaxel – first dose date of paclitaxel + 7)/7

Actual Dose Intensity (DI)

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

Relative Dose Intensity (RDI)

- Intended DI (mg/m^2/3-week cycle) = 240 (mg/m^2/3-week cycle)
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [240 (mg/m^2/3-week cycle)]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [240 (mg/m^2/3-week cycle)]

6.5.3.3. Exposure to paclitaxel Q3W

The dose level for paclitaxel Q3W is calculated as actual dose administered/m^2 (mg/m^2). The actual paclitaxel regimen (QW vs Q3W) is determined using the Cycle 1 Day 1 paclitaxel dose regimen.

Intended duration of treatment with paclitaxel Q3W (weeks) =

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

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

Duration of exposure to paclitaxel (weeks) =

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

Actual Dose Intensity (DI)

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

Relative Dose Intensity (RDI)

- Intended DI (mg/m^2/3-week cycle) = 175 (mg/m^2/3-week cycle)
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [175 (mg/m^2/3-week cycle)]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [175 (mg/m^2/3-week cycle)]

6.5.3.4. Exposure to carboplatin

The dose level for carboplatin is calculated as actual AUC administered.

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 in chemotherapy phase 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

Actual Dose Intensity (DI)

- By cycle actual DI (AUC/3-week cycle) = [cumulative dose in the cycle (AUC)]/[cycle duration (weeks)/3]
- 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) = d (AUC/3-week cycle)
- By cycle RDI (%) = 100 × [by cycle actual DI] / [intended DI]
  = 100 × [by cycle actual DI] / [d (AUC/3-week cycle)]
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [d (AUC/3-week cycle)]

where d= 5 or 6 depending on the glomerular filtration rate (GFR) method used for the Cycle 1 Day 1 carboplatin dose.

6.5.3.5. Dose reductions

Applicable to avelumab, paclitaxel, and carboplatin.

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 by treatment arm.

6.5.3.6. Dose delays

Applicable to avelumab, paclitaxel, and carboplatin.

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, where planned days are: 21 for carboplatin, 7 for paclitaxel QW regimen, 21 for paclitaxel Q3W regimen, 21 for avelumab in the chemotherapy phase, 14 for avelumab in the maintenance phase.

For patients taking IDS, the interval encompassing the IDS date (ie Dose (x-1) Date < surgery < Dose x Date) will not be considered for dose delay assessment.

Delays will be grouped into the following categories:

- No delay
- 1-3 days delays
- 4-6 days delay
- 7 or more days delay

For example, for avelumab, administered on a 2-week schedule, if one patient receives avelumab on Day 1, then the next avelumab administration date will be on Day 15; however, if the patient receives avelumab at Day 16, 17 or 18, this is considered as 1-3 days delay.

No delay and 1-3 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.

6.5.3.7. Infusion rate reductions

Applicable to avelumab, paclitaxel, and carboplatin.

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

6.5.3.8. Infusion interruptions

Applicable to avelumab, paclitaxel, and carboplatin.

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 arm.

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

Prior and concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page. Pre-medications for study drug will also be summarized separately from the 'Pre-Medication Treatment' eCRF page.

Summary of prior medications, summary of concomitant medications and summary of pre-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 prior or 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.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent anti-cancer therapies

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

Anti-cancer treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

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 arm.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period as defined in Section 3.5.1.

All analyses described 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 and finalized for analysis of the current studies data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan and finalized for analysis of the current studies data prior to DB lock).
- **Complications Related to Surgery (CRS):** CRS as collected on dedicated AE page.

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 arm, primary SOC and PT in decreasing frequency based on the frequencies observed for Arm C.

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 preferred term (PT) as event category and MedDRA primary system organ class (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 arm:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of avelumab
  - TEAEs leading to dose reduction of paclitaxel
  - TEAEs leading to dose reduction of carboplatin
  - TEAEs leading to interruption of avelumab
  - TEAEs leading to interruption of paclitaxel
  - TEAEs leading to interruption of carboplatin
  - TEAEs leading to discontinuation of avelumab
  - TEAEs leading to discontinuation of paclitaxel
  - TEAEs leading to discontinuation of carboplatin
  - TEAEs leading to discontinuation of any study drug
  - TEAEs leading to discontinuation of all study drugs
  - Related TEAEs leading to discontinuation of avelumab
  - Related TEAEs leading to discontinuation of paclitaxel
  - Related TEAEs leading to discontinuation of carboplatin
  - Related TEAEs leading to discontinuation of any study drug

  - Related TEAEs leading to discontinuation of all study drugs
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
  - irAEs
  - IRRs

- TEAEs by SOC and PT and worst grade
- Related TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT
- TEAEs Excluding SAEs, with frequency ≥ 5% in any treatment arm 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 arm:

- TEAEs leading to dose reduction of avelumab by SOC and PT
- TEAEs leading to dose reduction of paclitaxel by SOC and PT
- TEAEs leading to dose reduction of carboplatin by SOC and PT

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

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 6.5.3.6). 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 6.5.3.6).

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 arm:

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

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

In addition, 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 arm:

- TEAEs leading to both interruption and dose reduction of avelumab by SOC and PT
- TEAEs leading to both interruption and dose reduction of paclitaxel by SOC and PT
- TEAEs leading to both interruption and dose reduction of carboplatin by SOC and PT

This summary will take into account PTs with both actions as defined in Section 6.6.1, even though the actions may be captured for different PT records (ie, different onset for the PT with action "drug interrupted" and the PT with action "dose reduced").

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 arm:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- Related TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of paclitaxel by SOC and PT
- Related TEAEs leading to discontinuation of paclitaxel by SOC and PT
- TEAEs leading to discontinuation of carboplatin by SOC and PT
- Related TEAEs leading to discontinuation of carboplatin by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT
- Related TEAEs leading to discontinuation of any study drug by SOC and PT
- TEAEs leading to discontinuation of all study drugs by SOC and PT

- Related TEAEs leading to discontinuation of all study drugs 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 arm.

- 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 arm:

- 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 arm:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- irAEs leading to discontinuation of avelumab, by Cluster and PT
- irAEs leading to discontinuation of paclitaxel, by Cluster and PT
- irAEs leading to discontinuation of carboplatin, by Cluster and PT
- irAEs leading to discontinuation of any study drug, by Cluster and PT
- irAEs leading to discontinuation of all study drugs, 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 arm:

- IRRs leading to death, by PT
- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- IRRs leading to discontinuation of avelumab, by PT
- IRRs leading to discontinuation of paclitaxel, by PT
- IRRs leading to discontinuation of carboplatin, by PT
- IRRs leading to discontinuation of any study drug, by PT
- IRRs leading to discontinuation of all study drugs, by PT
- Serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later). For IV study drugs administered in combination, the infusion numbers are those associated with the regimen, rather than the individual study drugs.

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.

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

- CRSs leading to death, by PT
- CRSs, by PT
- CRSs, Grade ≥ 3, by PT
- CRSs leading to discontinuation of avelumab, by PT
- CRSs leading to discontinuation of paclitaxel, by PT
- CRSs leading to discontinuation of carboplatin, by PT
- CRSs leading to discontinuation of any study drug, by PT
- CRSs leading to discontinuation of all study drugs, by PT
- Serious CRSs, by PT

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

In addition the following analyses will be presented for Tier-1 (irAEs and IRRs as defined in Appendices 1 and 2) and Tier-2 events separately. P-values and CIs for risk difference will be calculated based on the unconditional exact method by Santner and Snell (1980). No additional analyses will be presented for Tier-3 AEs.

- Frequency (number and percentage) of patients with each of the following by treatment arm and PT or Clustered Term:
  - Tier-2 AEs
  - Tier-2 AEs Grade ≥ 3
- Point estimate for risk difference and 95% CI for risk difference (experimental arm vs comparator arm) for each of the following by PT or Clustered Term:
  - irAEs
  - irAEs Grade ≥ 3
  - IRRs
  - IRRs Grade ≥ 3
  - Tier-2 AEs
  - Tier-2 AEs Grade ≥ 3
- 2-sided p-value associated with risk difference (experimental arm vs comparator arm) for each of the following by PT or Clustered Term:
  - irAEs

- irAEs Grade ≥ 3
- IRRs
- IRRs Grade ≥ 3

- The p-values and CIs reported are not adjusted for multiplicity and should be used for screening purposes only. The 95% CIs are provided to help gauge the precision of the estimates for the risk difference and should be used for estimation purposes only.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. 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).

Quantitative data will be summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time (unscheduled measurements would therefore not be included in these summaries as described in Section 5.2.9). End of Treatment visit laboratory results will be summarized separately. The changes computed will be the differences from baseline. Qualitative data based on reference ranges will be described according to the categories (ie, Low, Normal, High).

Abnormalities classified according to NCI-CTCAE toxicity grading version 4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), 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 arm:

- 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 arms, 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 a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

Parameters with NCI-CTC 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 summary of laboratory parameters by CTCAE grade table will include number and percentage of patients with Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4), laboratory abnormalities during the on-treatment period.
- 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 above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils
- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH)

6.6.5.2. Other laboratory parameters

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

- Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT) and International Normalized Ratio (INR).
- Urinalysis: Protein, glucose, blood and albumin
- Other parameters: ACTH, TSH and free T4
- Pregnancy test

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.

In addition, listings of abnormal values will be provided for hematology, chemistry, urinalysis, coagulation parameters. If there is at least one abnormal assessment for any parameter, all the data for that laboratory parameter will be included into the listing.

For all tests not mentioned above but present in the clinical data, a listing of patients with at least one result for the relevant test will be provided.

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 in the Chemotherapy Phase, and Day 1, Day 15 and Day 29 of each cycle in the maintenance phase. Height will be measured at screening only.

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. QTcB and QTcF will be derived based on RR and QT (see below).

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. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of patients (eg >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression methods which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT

- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} \times (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

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 arm, 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, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- 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

Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

6.6.8. Physical examination

Abnormal findings in physical examination are recorded in the Medical history (at screening) or Adverse Event eCRF pages. No separate analysis will be performed for physical examination findings.

6.6.9. ECOG performance status

The ECOG shift from baseline to highest score during the on-treatment period will be summarized by treatment arm. ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

7. INTERIM ANALYSES

7.1. Introduction

The goals of the interim analyses are to allow early stopping of treatment arm(s) for futility or efficacy. The interim analysis of PFS and OS will be performed as described in Sections 5.1.1 and 5.1.2 using the methodology described in Section 6.1.1 for PFS and 6.2.2.1 for OS.

At the time of the interim analysis for PFS, the interim analysis for OS will be performed by an independent statistician. Unblinded results from the interim analysis for PFS and first interim analysis for OS will not be communicated to the Sponsor's clinical team or to any party involved in the study conduct (apart from the independent statistician and E-DMC members) until the E-DMC has determined that either (i) PFS analysis has crossed the pre-specified boundary for efficacy or (ii) the study needs to be terminated due to any cause, including futility or safety reasons. Further details will be described in the E-DMC charter.

At the time of final PFS analyses, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. All patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance the 3rd or 4th interim analysis).

7.2. Interim Analyses and Summaries

At each analysis time point, the critical boundaries for the group sequential test will be derived from the predefined spending function(s) as described in Section 5.1. The calculations of boundaries will be performed using EAST.

7.2.1. Interim analysis for PFS

Let $u(t_1)$ and $u(t_F)$ denote the upper critical boundaries based on the test statistics Z_1 and Z_F for efficacy at the interim and the final analysis, respectively, and let $l(t_1)$ and $l(t_F)$ denote the lower critical boundary for futility at the interim and final analysis, respectively. For the final analysis, $l(t_F)=u(t_F)$.

The critical values $u(t_1)$ and $l(t_1)$ for the interim analysis of PFS are determined such as

$$P_0(Z_1 \geq u(t_1)) = \alpha(t_1) \quad \text{and} \quad P_a(Z_1 \leq l(t_1)) = \beta(t_1) \ ,$$

where P_0 and P_a denote the probabilities under the null hypothesis and the alternative hypothesis, respectively, and $\alpha(t_1)$ and $\beta(t_1)$ denote the α and β spent, respectively, based on the predefined spending functions at information fraction t_1 (t_1 is calculated as the ratio of the number of PFS events observed at the time of the cut-off for the interim analysis and the total number of PFS events targeted for the final analysis).

The boundary for the final efficacy analysis will be calculated such that

$$\alpha(t_1) + P_0(Z_1 < u(t_1), Z_F \geq u_F) = 0.0125$$

As described in Section 5.1.2, if the number of PFS events in the final analysis deviates from the target number of PFS events, the final analysis criteria will be determined as above taking into account the actual alpha spent at the interim analysis and the actual correlation between the two test statistics Z_1 and Z_F, so that the overall 1-sided significance level across all analyses and comparisons is preserved at 0.025.

7.2.2. Interim analysis for OS

No futility analysis will be performed for OS. Let $u(t_i)$ and $u(t_F)$ denote the upper critical boundaries based on the test statistics Z_i and Z_F for efficacy at the i^{th} interim and the final analysis, respectively, where i=1, 2, 3, 4.

In what follows P_0 denotes the probability under the null hypothesis, and $\alpha(t_i)$ denotes the α spent based on the predefined α-spending function at information fraction t_i (t_i is calculated as the ratio of the number of OS events observed at the time of the cut-off for the i^{th} interim analysis and the total number of OS events targeted for the final analysis).

For each comparison, the critical value $u(t_1)$ for the 1st interim analysis of OS is determined such as

$$P_0(Z_1 \geq u(t_1)) = \alpha(t_1).$$

Critical boundaries for the additional interim analyses and the final analysis of OS are calculated recursively as follows for each comparison

$u(t_2)$ is derived such that $\alpha(t_1) + P_0(Z_1 < u(t_1), Z_2 \geq u(t_2)) = \alpha(t_2)$,

$u(t_3)$ is derived such that $\alpha(t_2) + P_0(Z_1 < u(t_1), Z_2 < u(t_2), Z_3 \geq u(t_3)) = \alpha(t_3)$,

$u(t_4)$ is derived such that $\alpha(t_3) + P_0(Z_1 < u(t_1), Z_2 < u(t_2), Z_3 < u(t_3) Z_4 \geq u(t_4)) = \alpha(t_4)$,

The boundary for the final efficacy analysis is derived such that

$$\alpha(t_4) + P_0(Z_1 < u(t_1), Z_2 < u(t_2), Z_3 < u(t_3), Z_4 < u(t_4), Z_F \geq u(t_F)) = 0.0125$$

As described in Section 5.1.2, if the number of OS events in the final analysis deviates from the target number of OS events, the final analysis criteria will be determined as above taking into account the actual alpha spent at the interim analyses and the actual correlation between the five test statistics Z_i (i=1, 2, 3, 4) and Z_F, so that the overall 1-sided significance level across all analyses and comparisons is preserved at 0.025.

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9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the Safety Review Plan (SRP) for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 20. This case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

Table 20 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'	
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) 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 Tables 21 and 22 (identified for IV drugs only).

Table 21 Case Definition for IRRs – IV study drugs Administered Alone

Condition	Selection criterion
If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2	• AE onset date = date of infusion of study drug AND • AE timing related to study drug ('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
4A	• AE onset date = date of infusion of study drug AND • AE timing related to study drug in ('DURING', 'AFTER')
4B	AE onset on the day after infusion

Table 22 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

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