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

JAVELIN OVARIAN 100

Compound:	MSB0010718C
Compound Name:	Avelumab*
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number (if applicable):	EudraCT 2015-003239-36
Protocol Number:	B9991010
Phase:	Phase 3

[redacted]

* Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C)

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Document History

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

[redacted]

PROTOCOL SUMMARY

Background and Rationale

Ovarian cancer (OC) is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. Fewer than 40% of women diagnosed with ovarian cancer are cured.[1] The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease.[2] Although expectations for long-term survival can be very high if the cancer is identified and treated early, women who are diagnosed with advanced ovarian cancer continue to have poor long-term survival due to refractory, resistant, or recurrent disease and most will die within 5 years.

Carboplatin in combination with paclitaxel is the current standard of care in the first-line epithelial ovarian cancer (EOC) treatment setting following debulking surgery for patients with stage IC or higher, as well as selected stage IA-B patients (those with high grade or clear cell histology). Chemotherapy is administered for a total of 6-8 cycles.[3] Complete response is achieved in approximately 75% of patients, but most patients ultimately succumb to the disease with median progression-free survival (PFS) of approximately 18 months.[4] Therefore, there remains a high unmet need for newer agents with novel mechanisms of action and combination regimens able to modify the natural history of the disease.

Recently, the dose-dense frontline chemotherapy regimen of weekly paclitaxel combined with Q3W carboplatin has been increasing in usage.[5,6]

The current standard of care in the frontline maintenance treatment setting is region-dependent. Some patients receive bevacizumab in combination with chemotherapy, followed by one year of bevacizumab maintenance in regions where bevacizumab is approved in this setting. For a significant number of newly diagnosed patients, the standard of care remains a platinum doublet chemotherapy followed by observation.

Programmed death ligand 1 (PD-L1, also called B7-H1 or CD274) has a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell functions.[7,9,10]

Avelumab* (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. In preclinical studies, the combination of avelumab with chemotherapy (gemcitabine, oxaliplatin, 5FU) showed improved anti-tumor activity over single-agent chemotherapy.[11] Preliminary data from the ongoing ovarian cancer Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004), showed an overall response rate (ORR) of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.[12]

*Avelumab is the proposed International Nonproprietary Name (INN) for the anti-PD-L1 monoclonal antibody (MSB0010718C)

Preliminary subgroup analysis demonstrated increased activity in patients with lower tumor burden, lower number of prior therapies, and platinum sensitivity.[12] Therefore, avelumab has the potential to change the natural history of disease in the maintenance setting following frontline chemotherapy, when tumor burden is small. Patients with minimal residual disease are thought of as the ideal candidates for immunotherapy approaches in ovarian cancer.[13]

In addition, there are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[14,15] Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[16,17,18] In summary, avelumab demonstrated promising antitumor activity in heavily pretreated patients with ovarian cancer and has the potential to improve the durability of response to platinum-based therapy in the frontline setting when combined with chemotherapy and in the maintenance setting.

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 progression free survival (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 each treatment arm in patients with previously untreated EOC including the assessment of treatment side effects and disease-related symptoms.

CCI [redacted]

- CCI [redacted]

- CCI [redacted]

Study Endpoints

Primary Endpoint

- Progression-free survival (PFS) as determined by blinded independent central review (BICR) by RECIST version 1.1

Secondary Endpoints

- Efficacy: Overall survival (OS), PFS by Investigator assessment as well as Objective response (OR), Duration of response (DR), Maintenance PFS by BICR assessments and Investigator assessment, pathological Complete Response (pCR), PFS2, and PFS by Gynecological Cancer Intergroup (GCIG) criteria
- Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs)
- Patient-Reported Outcomes: FOSI-18 and EuroQoL5 Dimension (EQ-5D-5L)
- Pharmacokinetics: 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
- Immunogenicity: anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against avelumab
- 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)

[redacted]

Exploratory Endpoints

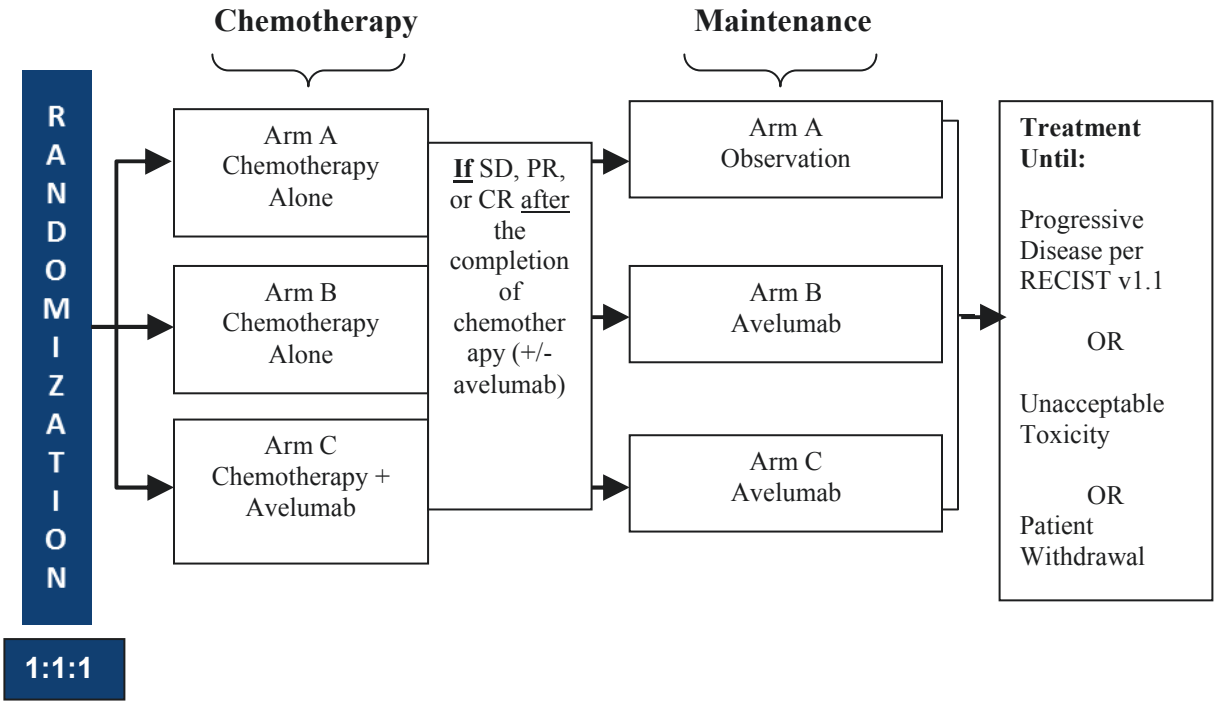
CCI

- CA-125 levels

CCI

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. Eligible patients must have previously untreated, histologically confirmed Stage III-IV epithelial ovarian (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) and be candidates for platinum-based chemotherapy. Patients must meet full eligibility criteria as specified in Section 4.



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 to the above treatment arms.

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 as described in Section 5.1. Crossover between treatment arms will not be permitted.

Intravenous carboplatin-paclitaxel will be used as the chemotherapy backbone, consisting of Q3-week (Q3W) carboplatin and the investigator choice of either Q3W or weekly paclitaxel (see below). Once a paclitaxel regimen is selected for a given patient, it should not be changed for the duration of the study.

Patients may be enrolled either following primary debulking surgery, or prior to initiation of neoadjuvant chemotherapy. The latter group will undergo interval debulking surgery after 3 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).

Study Treatments

The study period includes two treatment phases, the chemotherapy phase and the maintenance phase. For purposes of consistent on-study assessments, 1 study cycle is defined as 3 weeks (21 days) during the chemotherapy phase, and 6 weeks (42 days) during the maintenance phase.

In the **chemotherapy phase** of the study, study drugs are given as follows:

Arms A and B: The investigator will have the choice between weekly or Q3W paclitaxel:

- Paclitaxel 175 mg/m^2 intravenously (IV) over 3 hours, followed by carboplatin dose AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

  OR

- Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8, 15 plus carboplatin AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

Arm C:

- Chemotherapy (investigator's choice as referenced above) + avelumab 10 mg/kg administered as a 1-hour IV infusion once every 3 weeks for 6 cycles.

For patients who are enrolled prior to neoadjuvant therapy, the first 3 cycles will be administered prior to interval debulking surgery, and the remainder of chemotherapy will be administered after surgery. Upon completion of chemotherapy, patients without evidence of disease progression [stable disease (SD), partial response (PR), or complete response (CR)] will proceed to the maintenance phase of the study. Disease progression must be confirmed by BICR prior to withdrawal. At this point the assignment to Arms A or B will be unblinded.

In the **maintenance phase** of the study, patients randomized to Arms B or C will receive avelumab 10 mg/kg administered as a 1-hour IV infusion once every 2 weeks.

Patients will receive study treatment until confirmed progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or a maximum duration of 24 months (not including chemotherapy phase), whichever is earliest (see Section 6.5).

Patients who discontinue study treatment (or, if on Arm A maintenance, reach End of Treatment/Withdrawal) will be followed every 12 weeks for survival status until death or until study completion, whichever is earlier.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer.

Sample Size Determination

The study is designed to test, in parallel, two hypotheses:

- The first null hypothesis is that the true PFS hazard rate for both platinum-based chemotherapy alone followed by observation (Arm A), and avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance (Arm C), are the same (HR=1); versus the alternative hypothesis that the true hazard rate is smaller for Arm C than for Arm A (HR<1).

- The second null hypothesis is that the true PFS hazard rate for both, platinum-based chemotherapy alone followed by observation (Arm A), and platinum-based chemotherapy followed by avelumab maintenance (Arm B), are the same (HR =1); versus the alternative hypothesis that the true hazard rate is smaller for Arm B than for Arm A (HR<1).

Approximately 951 patients will be enrolled 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) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant. Two hundred and seventy-two (272) PFS events within each comparison will be required to have 90% power to detect a hazard ratio of 0.65 using a one-sided log-rank test at a significance level of 0.0125.

The median PFS for patients treated with platinum based chemotherapy alone followed by observation was estimated to be 23 months, based on the assumption that 50% of patients will receive dose-dense chemotherapy which was demonstrated in JGOG3016 to improve median PFS from 18 to 28 months.[6] The sample size for this study is determined based on the assumptions that treatment with avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance, or treatment with platinum-based chemotherapy followed by avelumab maintenance is expected to increase the median PFS to ≥ 35.4 months, corresponding to a hazard ratio (HR) of 0.65 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each treatment arm, 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 cutoff for the primary PFS analyses 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.

If the true HR is 0.65 under the alternative hypothesis, 272 PFS events within each comparison will be required to have 90% power to detect a HR of 0.65 using a one-sided log-rank test at a significance level of 0.0125 (total significance level one sided 0.025), 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 study will be considered positive if at least one of the primary objectives is met for the primary PFS endpoint.

[redacted]

SCHEDULE OF ACTIVITIES

The Schedule of Activities (SOA) table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol (Section 6 and Section 7) for detailed information on each procedure and assessment required for compliance with the protocol. Patients who are enrolled prior to neoadjuvant therapy will undergo interval debulking surgery during the chemotherapy phase as described in Section 5.6.3.1 and will resume on the schedule of assessments upon recovery.

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

Protocol Activities [1]	**Screening**	**Study Treatment**									**Post-Treatment**		
		Chemotherapy Phase (1 cycle = 3 weeks = 21 days)						**Maintenance Phase** [2] **(1 cycle = 6 weeks = 42 days)**					
		Odd cycles			**Even cycles**								
	≤28 Days Prior to Randomization	**Day 1 (±3 days)**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Day 1 (±3 days)**	**Day 15 (±3 days)**	**Day 29 (±3 days)**	**End of Treatment /Withdrawal** [3]	**Safety Follow-up (Days 30, 60, and 90 ± 3 days)** [4]	**Survival Follow-Up** [5]
Clinical Assessments													
Informed Consent [6]	X												
Medical/Oncological History [7]	X												
Physical Examination [8]	X	X			X			X	X [2]	X [2]	X		
Contraception Check [9]	X	X			X			X			X	X	
ECOG Performance Status	X	X						X			X	X	
Blood Pressure, Pulse Rate [10]	X	X			X			X	X [2]	X [2]	X		
Laboratory Studies													
Hematology [11]	X	X	X (for patients on QW paclitaxel)	X (for patients on QW paclitaxel)	X	X (for patients on QW paclitaxel)	X (for patients on QW paclitaxel)	X	X [2]	X [2]	X		

Protocol Activities [1]	Screening	Study Treatment									Post-Treatment		
		Chemotherapy Phase (1 cycle = 3 weeks = 21 days)						Maintenance Phase [2] (1 cycle = 6 weeks = 42 days)					
		Odd cycles			Even cycles								
	≤28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	End of Treatment /Withdrawal [3]	Safety Follow-up (Days 30, 60, and 90 ± 3 days)[4]	Survival Follow-Up [5]
Blood Chemistry [11,14]	X	X			X			X	X [2]	X [2]	X		
Coagulation [11]	X	X			X			X			X		
CA-125[12]	X	X			X			X			X		
BRCA 1/2 Mutation Status[13]	X												
Thyroid Function Tests + ACTH [15]	X	X						X (3rd cycle, then Q12 weeks thereafter)			X		
HBV and HCV	X							X (first cycle only)					
Serum/Urine Pregnancy Test [16]	X	X			X			X			X	X	
Urinalysis [17]	X							X					
12-Lead ECG [18]	X	X						X (first cycle only)					
Randomization and Study Treatment													
Randomization [19]	X												

Protocol Activities [1]	Screening	Study Treatment									Post-Treatment		
		Chemotherapy Phase (1 cycle = 3 weeks = 21 days)						Maintenance Phase [2] (1 cycle = 6 weeks = 42 days)					
		Odd cycles			Even cycles								
	≤28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	End of Treatment /Withdrawal [3]	Safety Follow-up (Days 30, 60, and 90 ± 3 days)[4]	Survival Follow-Up [5]
Paclitaxel weekly Administration [20]		X	X	X	X	X	X						
Paclitaxel Q3 week Administration [21]		X			X								
Carboplatin chemotherapy Administration [20, 21]		X			X								
Administration of Avelumab (Arms B and C) [22 23]		X			X			X	X	X			
Disease Assessments													
Tumor Assessments (including scans) [24]	X	Once after 3 cycles of chemotherapy						X (every other cycle)			X		
Other Clinical Assessments													
Adverse Events [25]		→ X →									X	X	
Concomitant Medications/Treatments [26]	X	→	→	→	→	→	→	→	→	→	X	X	
Other Samplings													
PK Blood Sampling for Paclitaxel Pharmacokinetics [27]					X (C2 only)								
PK Blood sampling for Carboplatin Pharmacokinetics [28]					X (C2 only)								

Protocol Activities [1]	Screening	Study Treatment									Post-Treatment		
		Chemotherapy Phase (1 cycle = 3 weeks = 21 days)						Maintenance Phase [2] (1 cycle = 6 weeks = 42 days)					
		Odd cycles			Even cycles								
	≤28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	End of Treatment /Withdrawal [3]	Safety Follow-up (Days 30, 60, and 90 ± 3 days)[4]	Survival Follow-Up [5]
PK Blood Sampling for Avelumab Pharmacokinetics [29]		X (Arm C only)	X (Arm C only; weekly paclitaxel only)	X (Arm C only; weekly paclitaxel only)	X (Arm C only)	X (Arm C only; weekly paclitaxel only)	X (Arm C only; weekly paclitaxel only)	X (Arms B and C only)	X (Arms B and C only; C1 only)	X (Arms B and C only;C1 only)	X		
Mandatory Archival FFPE Tumor Tissue Block [30]	X												
De Novo Tumor Biopsy [31]											X		
Banked Blood Biospecimen for Genotyping [32]	X												
Banked Blood Biospecimen for Exploratory Biomarker Assessments [33]		X			X (2nd and 4th cycles only)			X (1st and 2nd cycles only)	X (Arms B and C; 1st and 2nd cycles only)	X (Arms B and C; 1st and 2nd cycles only)	X		
Blood for Avelumab ADA (Immunogenicity) Testing [34]		X			X (Arm C only)			X (Arms B and C only)	X		X	X	
Patient-Reported Outcomes (FOSI-18 and EQ-5D-5L) [35]		X			X			X			X		X

Footnotes for Schedule of Activities
1. **Protocol Activities**: All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. Day 1 windows do not apply to Cycle 1 of chemotherapy or maintenance phases.
2. Maintenance Phase: Maintenance phase should begin within 4 weeks after the last dose of chemotherapy. The first visit of maintenance therapy will be numbered maintenance Cycle 1 Day 1 even if the last chemotherapy cycle was not completed. All maintenance Day 15 and Day 29 assessments for patients randomized to Arm A are optional.
3. **End of Treatment/Withdrawal**: Performed when criteria for treatment/observation or treatment discontinuation are met (Including Arm A). Obtain these assessments if not completed within the prior week, except for tumor assessments which need not be repeated if performed within the prior 6 weeks.
4. **Post-Treatment Safety Follow-up**: For patients receiving study treatment within 90 days prior to the End of Treatment (EOT)/Withdrawal visit, post-treatment safety follow-up must occur monthly for 90 days after the last dose of study treatment (Day 30 ± 3, Day 60 ± 3, Day 90 ± 3). The safety follow-up does not need to be performed for a patient who remains in maintainence and is undergoing safety assessments every 6 weeks.
5. **Survival Follow-up**: Post-study survival status will be collected every 12 weeks after EOT/Withdrawal visit until death or study closure, whichever occurs first. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.
6. **Informed Consent**: Must be obtained prior to undergoing any trial-specific procedure.
7. **Medical/Oncological History**: To include information on prior systemic chemotherapy regimens, surgery, and radiation therapy.
8. **Physical Examination**: Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at screening only).
9. **Contraception Check**: Patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly during the entire study treatment period including up to at least 60 days after the last avelumab infusion, and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient.
10. **Blood Pressure, Pulse Rate**: Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.
11. **Hematology, Blood Chemistry, and Coagulation**: No need to repeat on Day 1 of Cycle 1 if screening assessment performed within 7 days prior to that date. Required tests are listed in Table 11. May also be performed when clinically indicated.
12. CA-125: To be assessed locally. No need to repeat on Day 1 of Cycle 1 if screening assessment performed within 7 days prior to that date.
13. BRCA status. If BRCA1/2 mutation status is known or becomes known for a patient during the study, this information will be recorded in the CRF either at screening or at later visits. No BRCA1/2 testing is required for this study.
14. **Blood Chemistry**: Full chemistry panel (required tests are listed in Table 11) is required at screening, on Day 1 of each chemotherapy study cycle, and at End of Treatment/Withdrawal. Core chemistry panel (required tests are listed in Table 11) is required on Days 1, 15, and 29 of each maintenance cycle. If full and core chemistry panels are scheduled at the same visit, only the full chemistry will be performed. For patients with liver metastases at study entry, ALT, AST, total bilirubin, and alkaline phosphatase tests will be performed weekly in the first 6 weeks of treatment.
15. **Thyroid Function Tests and ACTH:** Baseline free T4, TSH, and ACTH will be performed at screening or at chemotherapy Cycle 1 Day 1 pre-dose. Subsequently, TSH and ACTH should be assessed during the chemotherapy phase on Day 1 of every other chemotherapy cycle. During the maintenance phase, TSH and ACTH should be assessed during 3rd Maintenance cycle, then every 12 weeks thereafter while on treatment; and at end of treatment visit. Free T4 should additionally be performed when clinically indicated. See Table 11.

16. **Serum/Urine Pregnancy Test**: For patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on two occasions prior to starting study therapy: once at the start of screening (all patients), and once before the administration of study treatment. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the End of Treatment/Withdrawal visit, during the post-treatment safety follow-up visits up to at least 60 days after the last avelumab infusion for patients receiving avelumab at EOT/withdrawal visit, and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRB/IECs or if required by local regulations (see Section 7.1.1).
17. **Urinalysis (**Table 11**):** Dipstick is acceptable. If urine dipstick is positive for urine blood, microscopic urinalysis will have to be done (Reflex Testing) and the patient will be treated as per local standard of care based on Investigator medical judgment. May also be performed when clinically indicated.
18. **12-lead ECG**: See Section 7.1.5 for details. All patients require a single ECG measurement at screening (clinically significant abnormal findings in baseline ECGs will be recorded as medical history and on Day 1 of every other cycle during chemotherapy after carbo/taxol infusion on Arms A and B and after Avelumab infusion on Arm C. Additional ECGs will be performed on Day 1 of first maintenance cycle and may be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
19. **Randomization**: Randomization operated by the Sponsor via an interactive response technology (IRT) system. Required information: site and patient identifiers, demographic, and stratification information. Study treatment must begin within 7 days after randomization. For patients randomized to a chemotherapy regimen that does not include avelumab, assignment to Arms A or B will remain blinded during the chemotherapy phase (see Section 5.1)
20. Study Treatment: Weekly Paclitaxel Administration: For additional information about pre-medications for paclitaxel, see Section 5.3.2.1. Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8 and 15 of each cycle, with carboplatin dose AUC 5 or AUC 6 as described in Section 5.3.2.2.2, IV on Day 1 of every cycle.
21. **Study Treatment: Q3W Paclitaxel Administration**: For additional information about pre-medications for paclitaxel, see Section 5.3.2.1. Paclitaxel 175 mg/m^2 IV over 3 hours, followed by carboplatin dose AUC 5 or AUC 6 as described in Section 5.3.2.2.2, IV on Day 1 of every cycle.
22. **Premedication for Avelumab:** Premedication with an antihistamine and with paracetamol/acetaminophen approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol/acetaminophen i.v. or oral equivalent). This may be modified based on local treatment standards and guidelines, as appropriate.
23. **Study Treatment: Avelumab (for patients randomized to Arms B and C)**: Patients will receive avelumab 10 mg/kg administered as a 1-hour IV infusion (see Section 5). Avelumab will be administered Q3W on Day 1 of every 3-week cycle during chemotherapy (if on Arm C) and Q2W during maintenance on Days 1, 15, and 29 of every 6-week maintenance cycle (if on Arm B or Arm C).

24. **Tumor Assessments:** Tumor assessment should be performed 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. Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or MRI scans. Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. CT or MRI scans to be done every 12 weeks (window of 7 days prior to dosing is allowed) until confirmed disease progression regardless of initiation of subsequent anti-cancer therapy. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or rising CA-125 levels), and at the EOT/Withdrawal visit (if not done in the previous 6 weeks). CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD in the absence of rapid clinical deterioration. Assessment of response will be made using RECIST v.1.1 (Appendix 3) CCI [redacted] All radiographic images will be collected and may be objectively verified by an independent third party core imaging laboratory as described in Study Manual. See Section 7.2 for additional information.
25. **Adverse Events**: Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03. See Section 8.2).
26. **Concomitant Medications/Treatments**: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to the end of treatment/withdrawal visit or the end of the safety follow-up period, whichever is later. For patients on Arm A maintenance, concomitant medications will be collected up to the point when treatment discontinuation criteria are met. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions). See Section 5.6 for further details.
27. **Blood Sampling for Paclitaxel Pharmacokinetics**: At selected sites, a 3.5 mL of whole blood will be collected in at least 10 patients in each of the 3 treatment arms, regardless of regimen, at pre-dose, and at 1, 3 4, 5, 6, 10, and 24 hours post-paclitaxel on Day 1 of Cycle 2. Note: the 1- and the 3-hour post-infusion samples represent the end of infusion samples for weekly and 3-weekly paclitaxel administration respectively and should be taken immediately before the end of infusion. Details are outlined in Section 7.4.
28. **Blood Sampling for Carboplatin (Total and Free Platinum) Pharmacokinetics**: At selected sites, a 5 mL whole blood will be collected in at least 10 patients in each of the 3 treatment arms at pre-dose and at, 0.5, and 1 (immediately before the end of infusion), 5, 6, 10, and 24 hours post-carboplatin infusion on Day1 of Cycle 2. Details are provided in Section 7.4.
29. **Blood Sampling for Avelumab Pharmacokinetics for all patients receiving avelumab**: **Chemotherapy Phase (Arm C only):** PK samples (3.5 mL) for avelumab will be collected within 2 hours prior to and immediately before the end of avelumab infusion (1 hour post-start of infusion) on Day 1of cycles 1-4. For patient's reciveing weekly paclitaxel only, an additional avelumab sample will be taken on Day 8 and Day 15 of Cycles 1-4 prior to the paclitaxel infusion. **Maintenance Phase (Arms B and C):** PK samples (3.5 mL) for avelumab will be collected within 2 hours prior to and immediately before the end of avelumab infusion (1 hour post-start of infusion) on Days 1, 15, and 29 of the first maintenance cycle. Thereafter, PK samples will be collected pre-dose and 1 hour post-start of infusion on Day 1 of every maintenance cycle until Cycle 18, at the end of treatment, and post-treatment safety follow up (30 Days) Details are provided in Section 7.4.

30. **Mandatory Archival FFPE Tumor Tissue Block**: A mandatory archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue block from initial diagnosis must be provided that is of sufficient size to allow, if possible, for sectioning of fifteen (15) 5-micron tissue sections. If an FFPE tumor tissue block cannot be provided, sites should provide fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accord with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted. For neoadjuvant patients, additional tumor collection for surgical specimen is described in Section 6.1.1.
31. ***De Novo* Tumor Biopsy**: A *de novo* (ie, fresh biopsy) tumor sample should be collected at End of Treatment if a patient signs a separate informed consent document and discontinues due to disease progression unless clinically contraindicated. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.
32. **Banked Blood Biospecimen for Genotyping**: A single 4-mL blood sample will be collected at Screening and retained in a biobank for possible pharmacogenetic assessments (ie, genotyping), unless prohibited by local regulations or by decision of the Institutional Review Board or Ethics Committee. Samples may be used for analyses of DNA sequence variation in genes potentially related to drug response, safety, PK, or mechanism of action (also see Section 7.6). This sample may also be collected on Day 1 prior to dosing if necessary.
33. CCI [redacted]
34. **Blood for Avelumab Immunogenicity Testing** (anti-avelumab antibodies; anti-drug antibodies [ADAs], **neutralizing anti-avelumab antibodies [NABs]**): All immunogenicity samples (3.5 mL) should be collected pre-dose and within 2 hours before the start of the avelumab infusion. **Chemotherapy Phase (Arm C only):** Immunogenicity sample (3.5 mL) will be collected predose on Day 1 of chemotherapy cycles 1-4. **Maintenance Phase** (**Arms B and C):** Immunogenicity samples (3.5 mL) will be collected predose on Days 1 and 15 of maintenance cycles 1 and 2. Thereafter, immunogenicity samples will be collected predose on Day 1 of every maintenance Cycle until cycle 18, at the end of treatment, and post-treatment safety follow up (30 Days). All samples that are positive for ADA may also undergo characterization for Nab. See Section 7.5.
35. **FOSI-18 and EQ-5D-5L**: All patients will complete these self-administered questionnaires pre-dose on Days 1 of every chemotherapy cycle, and on Day 1 of every maintenance cycle, at the EOT/Withdrawal visit, and every 6 weeks during the post-treatment safety and survival follow-up period for a total of 3 years from the date of patient enrollment. Patients must complete these questionnaires at the clinic prior to any study or medical procedure during the chemotherapy and maintenances phases, and at home every 6 weeks thereafter using an ePRO device, during the safety and survival follow-up period.
Abbreviations: → = ongoing/continuous event; ACTH = ;ADAs = anti-drug antibodies; AEs = adverse events; C = cycle; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Group; EOT = end of treatment; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; Nab = neutralizing antibody; PK = pharmacokinetics

1. INTRODUCTION

1.1. Indication

Avelumab is a fully human monoclonal antibody of the immunoglobulin (Ig) G1 isotype that is currently being investigated in patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.2. Background and Rationale

1.2.1. Ovarian Cancer

Ovarian cancer (OC) is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. Fewer than 40% of women diagnosed with ovarian cancer are cured.[1] The incidence of ovarian cancer increases with age and is most prevalent in the eighth decade of life. The median age at the time of diagnosis is 63 years, and 70% of patients present with advanced disease.[2] Although expectations for long-term survival can be very high if the cancer is identified and treated early, women who are diagnosed with advanced ovarian cancer continue to have poor long-term survival due to refractory, resistant, or recurrent disease and most will die within 5 years.

Ovarian neoplasms consist of several histopathological entities. Epithelial ovarian cancer (EOC) comprises the majority of malignant ovarian neoplasms (about 80%);[19] however, other less common pathologic subtypes must be considered in treatment recommendations. Fallopian tube cancer (FTC) and primary peritoneal cancer (PPC), which are less common neoplasms, are managed in a similar manner to epithelial ovarian cancer.

Carboplatin in combination with paclitaxel is the current standard of care in the first-line EOC treatment setting following debulking surgery for patients with stage IC or higher, as well as selected stage IA-B patients (those with high grade or clear cell histology). Chemotherapy is administered for a total of 6-8 cycles.[3] Complete response is achieved in approximately 75% of patients, but most patients ultimately succumb to the disease with median progression-free survival (PFS) of approximately 18 months.[4] Therefore, there remains a high unmet need for newer agents with novel mechanisms of action and combination regimens able to modify the natural history of the disease.

Recently, the dose-dense frontline chemotherapy regimen of weekly paclitaxel combined with Q3W carboplatin has been increasing in usage.[5,6] The Japanese Gynecologic Oncology Group (JGOG) 3016 study, conducted in previously untreated Stage II-IV patients with ovarian cancer, demonstrated improvement in PFS and OS compared to the traditional Q3W regimen. The toxicity profile was similar, with only anemia seen at a higher frequency with the weekly regimen. The GOG262[7] study was conducted to confirm these findings in the high-risk patient subgroup (Stage IV or suboptimal Stage III) and to examine the role of bevacizumab in this treatment setting. Patients were randomized to the dose-dense regimen vs traditional Q3W regimen. Within each treatment arm, patients were allowed to receive bevacizumab per physician's choice made prior to randomization. Approximately 80% of patients received bevacizumab. In the overall population, no benefit of weekly paclitaxel over Q3W regimen was demonstrated. However, pre-specified analysis in patients who did

not receive bevacizumab demonstrated statistically significant improvement in PFS in the dose-dense arm compared to Q3W regimen (Table 1). Therefore, GOG262 appears to confirm the benefit of weekly paclitaxel which was not realized in the presence of bevacizumab. Additional confirmatory studies, ICON8 and ICON8B, are ongoing.

At the present time, the dose-dense regimen is a category 1 National Cancer Comprehensive Network (NCCN) recommendation[3] and is the standard of care in Japan.

Several studies have been conducted in the frontline treatment setting (see Table 1). Due to long post-progression survival, PFS is an accepted endpoint in this setting.[7] Bevacizumab (Avastin®) demonstrated improvement in PFS in combination with chemotherapy followed by one year of maintenance therapy both in the first-line treatment setting[20,21] and in platinum-sensitive disease recurrence[22] but without an impact on overall survival (OS) in the overall patient population. Bevacizumab is currently approved in both the frontline and the platinum-resistant treatment settings in Europe, while in the US, it is approved only in the platinum-resistant treatment setting.

Table 1. Summary of Studies Demonstrating Benefit of Dose-Dense Frontline Chemotherapy and Related Studies

Study	Eligibility	Design Initial Treatment → Maintenance (1 year)	mPFS (months)	mOS (months)
ICON 7 N=1528	Stage III/IV or High-Grade stage I/II	Carbo-Q3W Paclitaxel-Bevacizumab → Bevacizumab vs. Carbo-Q3W Paclitaxel	20 (16 in HR**) vs. 17.5 (10.5 in HR**)	58 vs. 58
JGOG 3016 N=631	Stage II – IV	Carbo – Q3W Paclitaxel vs. Carbo - weekly Paclitaxel	17.5 vs. 28.2	62 vs. 100
GOG 218 N=1873	Suboptimal Debulking Stage III or Stage IV	Carbo-Q3W Paclitaxel - Bevacizumab → Bevacizumab vs. Carbo-Q3W Paclitaxel - Bevacizumab vs. Carbo-Q3W Paclitaxel	14* vs. 10 vs. 11	40 vs. 39 vs. 39
GOG 262 N=692	Suboptimal Debulking Stage III or Stage IV	Carbo – Q3W Paclitaxel vs. Carbo – weekly Paclitaxel vs. Carbo – Q3W Paclitaxel + Bevacizumab vs. Carbo - weekly Paclitaxel + Bevacizumab	10.3 vs. 14.2 vs. 15 vs. 15	

** High risk = FIGO Stage IV disease or FIGO Stage III disease and >1.0 cm of residual disease after debulking surgery

Neoadjuvant chemotherapy is also increasing in usage and is currently selected for 25% of patients with Stage II disease, 40% of patients with Stage III disease, and 50% of patients with Stage IV disease.[23] A randomized study demonstrated non-inferiority of this approach with respect to overall survival compared to adjuvant therapy in high-risk patients.[24] Typically, 3 cycles of chemotherapy are administered before surgery and 3 cycles after surgery. The same chemotherapy regimens are used in the neoadjuvant treatment setting as for the traditional post-surgical approach.[3] Other frontline studies have successfully enrolled patients undergoing either adjuvant or neoadjuvant therapies (GOG262 and ICON8).

The current standard of care in the frontline maintenance treatment setting is region-dependent. Some patients receive bevacizumab in combination with chemotherapy, followed by one year of bevacizumab maintenance therapy in regions where bevacizumab is approved in this setting. For a significant number of newly diagnosed patients, the standard of care remains a platinum doublet chemotherapy followed by observation.

1.2.2. Pharmaceutical and Therapeutic Background

1.2.2.1. Avelumab (MSB0010718C)

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

Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD 1. Unlike anti-PD-1 antibodies that target T cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD L2/PD 1 pathway intact to promote peripheral self-tolerance.[25] For complete details of the in vitro and nonclinical studies, refer to the Investigator's Brochure for avelumab.[11]

Avelumab is being developed jointly by Pfizer and Merck KGaA. The clinical development program for avelumab currently includes 5 ongoing studies in patients with various solid tumors conducted by Merck KGaA CCI CCI (2 ongoing Phase 1 studies in patients with solid tumors EMR 100070-001 and EMR 100070-002, a Phase 2 study in patients with Merkel cell carcinoma EMR 100070-003, and 2 Phase 3 studies in patients with non-small cell lung cancer (NSCLC) EMR 100070-004 and EMR100070-005). In addition to these trials, Pfizer is planning to conduct studies of avelumab in patients with ovarian cancer (B9991009 and B9991010 CCI), urothelial cancer (B9991001 C CCI), renal cell cancer (B9991002 and B9991003 CCI), NSCLC (B9991005 CCI), classical Hodgkin lymphoma (B9991007 CCI), and a variety of solid tumors (B9991004 CCI).

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

As of June 2015, treatment emergent adverse events occurred in all 53 patients (100.0%) participating in the dose escalation cohort, of which 42 patients (79.2%) reported treatment-related treatment-emergent adverse events (TEAEs). The most frequently observed treatment related TEAE was fatigue reported in 20 patients (37.7%), followed by influenza-like illness in 10 patients (18.9%), and pyrexia in 7 patients (13.2%).

Nine of the 53 patients (17.0%) in the dose escalation cohort experienced at least one Grade ≥ 3 treatment-related TEAE. These included event terms of autoimmune disorder (3 patients; 5.7%), aspartate aminotransferase (AST) increased and blood creatine phosphokinase (CPK) increased (each in 2 patients; 3.8%), and fatigue, abdominal pain lower, lipase increased, amylase increased, alanine aminotransferase (ALT) increased, blood alkaline phosphatase increased, and lymphocyte count decreased (each in 1 patient; 1.9%).

Of the 9 patients (17.0%) who had Grade ≥ 3 treatment-related TEAEs, 7 (13.2%) had Grade 3 events, 2 (3.8%) had Grade 4 events (blood creatine phosphokinase increased and autoimmune disorder), and no Grade 5 treatment-related TEAEs were observed.

Overall, the TEAE profile was similar across different dose escalation cohorts and the incidences of TEAEs by TEAE category did not increase with increasing dose.

1.2.2.2. Safety

As of 01 June 2015, safety data of 717 patients who were treated with 10 mg/kg of avelumab every 2 weeks and followed up for at least 4 weeks in the pooled tumor expansion cohort of Trial EMR 100070-001 were evaluated. In addition, safety data from the patients enrolled in the pooled expansion cohort were also evaluated by tumor type: cohorts for non-small cell lung cancer [NSCLC] (n=184), gastric cancer (n=120), ovarian cancer (n=75, see below) and urothelial carcinoma (n=44).

Of the 717 patients treated in the pooled expansion cohorts, 218 (45.4%) experienced at least 1 Grade ≥ 3 treatment emergent adverse event TEAE, and 330 (68.8%) reported treatment-related TEAEs, of which 59 (12.3%) reported Grade ≥ 3 treatment-related TEAEs.

The frequently reported (incidence ≥ 2% in the pooled expansion cohort) treatment-related TEAEs (any grade) in the pooled expansion cohort and the ovarian tumor expansion cohort are summarized in Table 2. The most frequently reported (occurring in at least 2 patients in the pooled extension cohort) Grade ≥ 3 treatment-related TEAEs in the pooled expansion cohort and the ovarian cancer expansion cohort are presented in Table 3.

Treatment-related TEAEs were observed in 498 (69.5%) patients in the pooled expansion cohort. The most frequently observed treatment-related TEAEs (with an incidence of ≥ 2%) of any grade in the pooled expansion cohort were infusion-related reaction (18.7%), fatigue (18.1%), nausea (10.3%), diarrhea (6.8%), chills (6.7%), and decreased appetite (5.2%). Other frequently seen treatment-related TEAEs with an incidence < 5% but ≥ 2% included arthralgia, pyrexia, hypothyroidism, pruritus, vomiting, influenza-like illness, rash, anemia, AST increased, myalgia, asthenia, headache, ALT increased, dyspnea, and constipation (Table 2).

Grade ≥ 3 treatment-related TEAEs were observed in 77 patients (10.7%) in the pooled expansion cohort (6.7% in the ovarian cancer expansion cohort). As shown in Table 3, the most frequently observed Grade ≥ 3 treatment-related TEAEs in the pooled expansion cohort were gamma-glutamyltransferase increased, infusion-related reaction, and lipase increased (each occurred in 7 patients; 1.0%), followed by anemia (6 patients; 0.8%), fatigue (5 patients; 0.7%), and AST increased and autoimmune hepatitis (each occurred in 4 patients; 0.6%). Other Grade ≥ 3 treatment-related TEAEs that were observed in ≥ 2 patients included ALT increased, lymphocyte count decreased, and pneumonitis (each in 3 patients; 0.4%), and asthenia, blood alkaline phosphatase increased, blood creatine phosphokinase increased, colitis, constipation, dyspnea, hyperglycemia, hypokalemia, hypoxia, myositis, and platelet count decreased (each in 2 patients; 0.3%).

Of the 77 patients (10.7%) who experienced Grade ≥ 3 treatment-related TEAEs, 60 (8.4%) had Grade 3 events, and 14 (2.0%) and 4 (0.6%) reported Grade 4 and Grade 5 treatment-related TEAEs, respectively.

No Grade 4 or 5 treatment-related TEAEs were reported for any patient in the ovarian cancer expansion cohort.

The 14 patients reporting Grade 4 treatment-related TEAEs included 7 patients (3.8%) in the NSCLC expansion cohort with the preferred terms (PTs) of infusion-related reaction (2 patients), amylase increased, embolic stroke, frontal lobe epilepsy, monoplegia, syncope, dyspnea, pneumonitis, and autoimmune neutropenia (each in 1 patient). Further Grade 4 treatment-related TEAEs were seen in 5 patients of the metastatic breast cancer (MBC) expansion cohort (3.0%) with the PTs of gamma-glutamyltransferase increased, hypokalemia, respiratory failure, anemia, neutropenia, thrombocytopenia, and cardiac arrest (each in 1 patient). The other 2 patients who reported Grade 4 treatment-related TEAEs were 1 patient in the mesothelioma expansion cohort (blood creatine phosphokinase increased) and 1 patient in the urothelial carcinoma expansion cohort (myositis).

The 4 patients who experienced Grade 5 treatment-related TEAEs were 2 patients in the NSCLC expansion cohort (radiation pneumonitis PPD and acute respiratory failure PPD) and 2 patients in the MBC expansion cohort (respiratory distress PPD and acute hepatic failure PPD).

Table 2. Most Frequently Reported (Incidence ≥ 2%) Treatment-Related TEAEs in the Pooled Expansion Cohorts and in the Ovarian Cancer Expansion Cohort (Any Grade)

MedDRA PT	Pooled Expansion Cohort Patients (n=717), n (%)	Ovarian Cancer Expansion Cohort (n=75), n (%)
Number of patients with at least 1 TEAE	498 (69.5)	55 (73.3)
Infusion related reaction	134 (18.7)	8 (10.7)
Fatigue	130 (18.1)	11 (14.7)
Nausea	74 (10.3)	10 (13.3)
Diarrhea	49 (6.8)	10 (13.3)
Chills	48 (6.7)	7 (9.3)
Decreased appetite	37 (5.2)	3 (4.0)
Arthralgia	35 (4.9)	2 (2.7)
Pyrexia	34 (4.7)	3 (4.0)
Hypothyroidism	32 (4.5)	5 (6.7)
Pruritis	28 (3.9)	2 (2.7)
Vomiting	28 (3.9)	5 (6.7)
Influenza-like illness	26 (3.6)	3 (4.0)
Rash	24 (3.3)	6 (8.0)
Anemia	21 (2.9)	1 (1.3)
Aspartate aminotransferase increased	20 (2.8)	1 (1.3)
Myalgia	20 (2.8)	3 (4.0)
Asthenia	18 (2.5)	0
Headache	18 (2.5)	2 (2.7)
Alanine aminotransferase increased	17 (2.4)	1 (1.3)
Dyspnea	17 (2.4)	2 (2.7)
Constipation	15 (2.1)	4 (5.3)

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment emergent adverse event.
Safety Population. Only TEAEs started during the on-treatment period are summarized

[redacted]

Table 3. Most Frequently Reported (in ≥ 2 Patients) Grade ≥ 3 Treatment-Related TEAEs in the Pooled Expansion Cohorts and in the Ovarian Cancer Expansion Cohort

MedDRA PT	Pooled Expansion Cohort Patients (n=480), n (%)	Ovarian Cancer Expansion Cohort (n=75), n (%)
Number of patients with at least 1 TEAE	77 (10.7)	5 (6.7)
Gamma-glutamyltransferase increased	7 (1.0)	0
Infusion related reaction	7 (1.0)	0
Lipase increased	7 (1.0)	1 (1.3)
Anemia	6 (0.8)	0
Fatigue	5 (0.7)	0
Aspartate aminotransferase increased	4 (0.6)	0
Autoimmune hepatitis	4 (0.6)	0
Alanine aminotransferase increased	3 (0.4)	0
Lymphocyte count decreased	3 (0.4)	0
Pneumonitis	3 (0.4)	0
Asthenia	2 (0.3)	0
Blood alkaline phosphatase increased	2 (0.3)	0
Blood creatinine phosphokinase increased	2 (0.3)	1 (1.3)
Colitis	2 (0.3)	0
Constipation	2 (0.3)	0
Dyspnea	2 (0.3)	0
Hyperglycemia	2 (0.3)	1 (1.3)
Hypokalemia	2 (0.3)	0
Hypoxia	2 (0.3)	0
Myositis	2 (0.3)	1 (1.3)
Platelet count decreased	2 (0.3)	0

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; TEAE: treatment emergent adverse event.
Safety Population. Only TEAEs started during the on-treatment period are summarized.

As of 01 June 2015, 289 of 717 patients (40.3%) in the pooled expansion cohorts had at least 1 serious TEAE. Treatment-related serious TEAEs were reported in 47 of 717 patients (6.6%) in the pooled expansion cohort. These included infusion-related reaction and pneumonitis (each in 6 patients; 0.8%), pyrexia (4 patients; 0.6%), autoimmune hepatitis and dyspnea (each in 3 patients; 0.4%), and colitis and non-cardiac chest pain (each in 2 patients; 0.3%). All other treatment-related serious TEAEs were reported in a single patient (0.1%) only. The incidence of treatment-related serious TEAEs was 4.0%, in the ovarian cancer expansion cohort.

As of 01 June 2015, 290 deaths (40.4%) occurred in the pooled expansion cohorts regardless of the cancer type. Twenty-seven (27) patients died in the ovarian cancer expansion cohort (36.0%).

The majority of deaths in the pooled expansion cohort were due to progressive disease (216 patients; 30.1%). In the pooled expansion cohort, overall, a total of 4 deaths (0.6%) for TEAEs related to trial treatment were considered as primary reason of the death by the

investigator. Two additional cases of death were reported and assessed as treatment-related, but the treatment related TEAEs were not considered as the primary reason of the death. Overall, of these 6 treatment-related deaths, 2 occurred in the NSCLC cohort, 3 occurred in the MBC cohort, and 1 occurred in the gastric cancer expansion cohort. A total of 81 deaths (11.3%) occurred within 30 days of last treatment in the pooled expansion cohort.

As of 01 June 2015, 139 patients (19.4%) in the pooled expansion cohort discontinued avelumab treatment for TEAEs. Of these patients with treatment discontinuations, 60 patients (8.4%) in the pooled expansion cohorts had treatment discontinuations that were due to treatment related TEAEs.

In the pooled expansion cohort, treatment-related events leading to treatment discontinuation were infusion-related reaction (19 patients; 2.6%), followed by gamma-glutamyltransferase increased (5 patients; 0.7%), autoimmune hepatitis, blood creatine phosphokinase increased, and lipase increased (3 patients; 0.4%), and dyspnea (2 patients; 0.3%). All other treatment-related TEAEs leading to treatment discontinuation were observed in a single patient (0.1%) only.

Treatment-related TEAEs leading to treatment discontinuation were reported in 13.3% patients in the ovarian cancer expansion cohort.

Immune-related Adverse Events: As of 01 June 2015, a cumulative review revealed 106 patients with potential irAEs out of717 patients (14.8%) treated in the pooled expansion cohort of Trial EMR 100070-001 and 8 patients out of 53 patients (15.1%) treated in the dose escalation cohort of Trial EMR 100070-001.

Treatment-related potential irAEs were observed in 71 of 717 patients (9.9%) in the pooled expansion cohort, and the incidence was 10.7% in the ovarian cancer expansion cohorts.

Hypothyroidism was the most frequent treatment-related irAE, which occurred in 32 patients (4.5%) in the pooled expansion cohort. The other frequent irAEs, which were considered as treatment-related, were pneumonitis (8 patients; 1.1%), autoimmune hepatitis and hyperthyroidism (4 patients; 0.6%), and colitis and dry eye (3 patients each; 0.4%). Additional treatment-related irAEs were seen in 2 or 1 patients in the pooled expansion cohort.

The majority of irAEs were Grade 1 or Grade 2 events. In the pooled expansion cohort, the Grade 3 and Grade 4 events occurred in 1.7% and 1.1% of patients, respectively, for all potential irAEs and in 1.4% and 0.6% of patients, respectively, for treatment-related irAEs. One patient PPD in the NSCLC expansion cohort had a Grade 5 irAE radiation pneumonitis, which was considered treatment-related by the investigator. In addition, 2 events of suspicion of autoimmune hepatitis (not confirmed by biopsy/autopsy) assessed as Grade 3 had a fatal outcome.

The potential irAE cases with a fatal are described in the avelumab IB.[11]

Infusion-related Reactions: Two Grade 4 unexpected serious adverse reactions (anaphylactic reaction and infusion-related reaction) involving 2 patients enrolled in Trial EMR 100070-001 reported in December 2013 triggered a cumulative review of serious and non-serious cases of infusion-related reactions/hypersensitivity reactions across the program. Following evaluation of the safety signal of infusion-related reactions/hypersensitivity reactions, the Sponsor decided to classify infusion-related reactions/hypersensitivity reactions as a newly identified risk (previously classified as a potential risk) and to implement a mandatory premedication with an antihistamine plus paracetamol (acetaminophen) for all patients beginning on 29 January 2014.

An event was considered an infusion-related reaction if (1) the event had the preferred term of "infusion-related reaction, drug hypersensitivity, or anaphylactic reaction" and (2) the onset of the event was on the same day or the next day following avelumab administration.

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

In addition, 4 patients (7.5%) in the dose escalation cohort reported an infusion-related reaction (all Grade 2).

After introduction of the mandatory premedication on 29 January 2014, 35 and 677 patients in the dose escalation and the pooled expansion cohorts of Trial EMR 100070-001 received trial treatment, respectively. Under this premedication procedure, 117 of 677 patients (17.3%) in the pooled expansion cohort experienced infusion-related reaction, with 28 patients (4.1%) having Grade 1, 86 patients (12.7%) having Grade 2, and 3 patients (0.4%) having Grade 3 event. No Grade 4 infusion-related reaction was observed after introduction of the mandatory premedication. Three patients (8.6%) in the dose escalation cohort reported infusion-related reactions (all Grade 2) starting from 29 January 2014.

In addition to the aforementioned cases of infusion-related reaction, 1 patient in the MBC expansion cohort PPD experienced Grade 4 cardiac arrest 1.5 hours after the third infusion of avelumab (10 mg/kg). This patient died from anoxic brain injury (not treatment related) after the cardiac arrest.

The management of infusion-related reactions and severe hypersensitivity reactions can be found in Section 5.3.5, respectively. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf.

1.2.2.3. Pharmacokinetics of Avelumab

Avelumab pharmacokinetics and dose proportionality following the first 1-hour infusion have been characterized in 77 Caucasian patients treated in the dose escalation and expansion cohorts of Study EMR 100070-001 by standard non-compartmental analysis. This analysis revealed that the exposure parameters of C_{max} and AUCτ generally increased in a dose proportionate fashion across the 1, 3, 10, and 20 mg/kg doses. Apparent half-life tended to increase with dose, likely due to the partial contribution of target mediated disposition at lower doses. Terminal half-life of 10 and 20 mg/kg doses were similar (102-120 hours, which likely indicates high target occupancy and low target mediated elimination. In a Phase 1 study in 17 Japanese patients (EMR 100070-002), exposures at 3, 10, and 20 mg/kg were similar to those observed in study EMR 100070-001.

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

1.2.2.4. Efficacy of Avelumab in Patients with Ovarian Cancer

The efficacy analysis of the ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last patient who was included in this pre-planned interim analysis on this expansion cohort. The ovarian cancer expansion cohort enrolled and treated a total of 75 patients. This cohort consisted of patients with recurrent or refractory ovarian cancer who had progression within 6 months of platinum-based therapy or progression after subsequent therapy in previously relapsed patients.

Table 4 presents the best overall response (BOR) results of 75 patients in the ovarian cancer expansion cohort, together with the ORR according to RECIST 1.1, defined as the proportion of patients with a BOR (confirmed or unconfirmed) of PR or CR. Of note, results of 8 patients (10.7%) were non-evaluable. The reasons for non-evaluable tumor response results included data missing or not assessable.

The ORR based on confirmed and unconfirmed responses for patients treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 patiens). In 5 of the 8 responders (62.5%), the responses were ongoing at the time of the data cutoff. The onset of the response was at around 6 weeks in 4 patients. The onset of the other 4 responders occurred at Weeks 10, 11, 14, and 18, respectively.

The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% CI: 6.3 to12.0 weeks).

Table 4. Unconfirmed Tumor Response Observed in Ovarian Cancer Expansion Cohort

BOR by RECIST 1.1 (Unconfirmed)	Ovarian Cancer Expansion Cohort (n=75) n (%)
Complete Response	0
Partial Response	8 (10.7)
Stable Disease	33 (44)
Progressive Disease	26 (34.7)
Non-Evaluable [a]	8 (10.7)
ORR (%, [95% CI])	8 (10.7)

BOR: best overall response; CI: confidence interval; ORR: objective response rate; RECIST: Response Evaluation Criteria in Solid Tumors.
a Non-evaluable includes 'missing' and 'not assessable'
Objective response rate was defined as proportion of patients with best overall response of CR or PR

Complete information for avelumab may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure for avelumab.[11]

1.2.2.5. Carboplatin and Paclitaxel for Ovarian Cancer

The combination of carboplatin and paclitaxel is one of the most widely used chemotherapy regimens and remains a global standard of care for frontline treatment of EOC. The traditional regimen consists of paclitaxel 175 mg/m^2 over 3-hour IV infusion, followed by carboplatin, administered at an area under the curve (AUC) of 5-7.5 intravenously over 1 hour on Day 1, given every 3 weeks for 6 cycles.[3] In the overall patient population, including Stage II-IV patients, this regimen is associated with response rates over 75%, PFS approximately 18 months and OS approximately 55 months.[6,26] The dose-dense regimen (as per JGOG 3016) consists of paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8, and 15, and carboplatin administered at an area under the curve (AUC) of 6 intravenously over 1 hour on Day 1, given every 3 weeks for 6 cycles. Compared to traditional Q3W paclitaxel-carboplatin, the dose-dense regimen was associated with significant improvement of PFS (28.2 months vs 17.5 months; hazard ratio [HR] 0.76, 95% CI 0.62–0.91; p=0.0037) and OS (100.5 months vs 62.2 months, HR = 0.79, 95% CI 0.63-0.99, p=0.039).[6] The adverse event profile was similar for these two regimens. Most common Grade 3/4 toxicities included neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, fatigue, arthralgia, myalgia, and neuropathy. With the exception of Grade 3/4 anemia which was higher in the dose-dense group (69% vs 44%), no significant differences in the adverse event profiles were seen.[5]

Complete information for carboplatin and paclitaxel may be found in the single reference safety documents, (which for this study are the Paraplatin® and Taxol® United States Prescribing Information (USPI), respectively).

1.2.2.5.1. Paclitaxel Pharmacokinetics

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a randomized Phase 3 study in ovarian cancer patients. It appeared that with the 24-hour infusion of paclitaxel, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{max} by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC (0-∞) were increased by 68% and 89%, respectively. In a study of weekly administration of paclitaxel following a 1-hour infusion of 60, 70, 80, and 90 mg/2, paclitaxel exposures increased in a dose proportional manner.[27]

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicated that between 89%-98% of drug is bound.

After intravenous administration of 15-275 mg/m2 doses of paclitaxel injection, as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m^2 dose of radiolabeled paclitaxel as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxy-paclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤2 times upper limit of normal (ULN) administered 175 mg/m2 was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m^2), but no observed increase in plasma exposure. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

1.2.2.5.2. Carboplatin (Total and Free) Pharmacokinetics

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 mg/m^2 to 500 mg/m^2 of carboplatin. The initial plasma half-life (alpha) was found to be

1.1 to 2 hours, and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours. The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration versus time curves from 0 to infinity (AUC inf) increased linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 mg/m^2 to 500 mg/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3% to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min, the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients.

The primary determinant of carboplatin injection clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients.

1.2.3. Rationale for Studying Avelumab in Patients with Previously Untreated Epithelial Ovarian Cancer

Programmed death ligand 1 (PD-L1, also called B7-H1 or CD274) has a known role in the suppression of T-cell responses. The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals to inhibit T-cell functions.[7,9,10]

Avelumab (MSB0010718C), a fully human antibody of the immunoglobulin G1 (IgG1) isotype, specifically targets and blocks PD-L1, the ligand for PD-1 receptor. Preliminary data from the ongoing ovarian cancer Study EMR 100070-001, which is being conducted by Merck KGaA/EMD Serono (EudraCT number 2013-002834-19, NCT01772004), showed an ORR of 10.7% (8/75) and stable disease in an additional 44% (33/75) of patients with advanced ovarian cancer.[12]

Preliminary subgroup analysis demonstrated increased activity in patients with lower tumor burden, lower number of prior therapies, and platinum sensitivity.[12] Therefore, avelumab has the potential to change the natural history of disease in the maintenance setting following frontline chemotherapy, when tumor burden is small. Patients with minimal residual disease are thought of as the ideal candidates for immunotherapy approaches in ovarian cancer.[13]

In addition, there is emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[14,15] Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants by dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[16,17,18] Certain chemotherapy agents including platinums are mutagenic.[28] Therefore, treatment with chemotherapy may create a pro-immunogenic, hypermutated state that may be optimal for activity of checkpoint inhibitors. In preclinical studies, the combination of avelumab with chemotherapy (gemcitabine, oxaliplatin, 5FU) showed improved anti-tumor activity over single-agent chemotherapy.[11]

Several checkpoint inhibitors have been combined with chemotherapy agents. The addition of ipilimumab to dacarbazine led to an improvement in overall survival in previously untreated melanoma compared to dacarbazine alone.[29] Ipilimumab was combined with platinum doublet chemotherapy in small cell as well as non-small cell lung cancer with encouraging results.[30,31] Combinations of PD1 blockers (pembrolizumab, nivolumab) as well as PDL1 blocker (atezolizumab) with platinum doublet chemotherapy demonstrated acceptable safety profiles with early evidence of clinical activity which appears to be higher than expected for platinum doublet therapy alone, particularly for atezolizumab.[31-35]

In summary, avelumab demonstrated promising antitumor activity in heavily pretreated patients with ovarian cancer and has the potential to improve the durability of response to platinum-based therapy in the frontline setting when combined with chemotherapy and in the maintenance setting.

1.2.4. Study Design Rationale

1.2.4.1. Study Population

Frontline chemotherapy in ovarian cancer is associated with high response rates but the majority of patients experience disease recurrence. Therefore, various novel therapeutic approaches have been aimed at reducing the risk of recurrence in the maintenance setting and therefore modifying the natural history of disease.[20,31] To date, for many patients, observation remains the standard of care following 6 cycles of frontline chemotherapy, and there is a high need for effective maintenance therapies. For this reason, the study is being conducted in the frontline setting.

Two large randomized studies demonstrated non-inferiority in terms of PFS and OS of the neoadjuvant approach to the traditional adjuvant approach, EORTC 55971 and CHORUS.[24, 70] There are no data to suggest whether the adjuvant or neoadjuvant treatment is the preferred setting to explore the addition of avelumab to chemotherapy. Therefore, in the current study, both neoadjuvant and adjuvant patients will be eligible. Patients enrolled in the neoadjuvant setting must fulfill eligibility criteria of the EORTC 55971 and CHORUS studies as described in the eligibility criteria of this protocol in Section 4.

1.2.4.2. 3-Arm Design

The current study is designed to evaluate the efficacy of avelumab in the maintenance setting following frontline chemotherapy (Arm B), as well as avelumab given concurrently with chemotherapy followed by avelumab maintenance (Arm C), compared to chemotherapy alone followed by observation (Arm A). Patients are randomized in a 1:1:1 ratio to one of 3 arms (A, B, or C). To prevent biased discontinuation during the chemotherapy portions of Arms A and B, assignment to these arms will be blinded until the start of maintenance therapy.

1.2.4.3. Study Endpoints

The primary endpoint of the study is PFS which is an accepted endpoint in the frontline setting.[32] Primary efficacy analysis will be performed from randomization according to the intention-to-treat principle. Secondary analysis will evaluate PFS from the start of maintenance therapy.

Other efficacy endpoints include overall survival (OS), objective reponse (OR), and duration of response (DR). This study will also include additional efficacy endpoints, PFS2, pathological complete response (pCR) and PFS by GCIG criteria, as defined below.

PFS2: PFS2 is defined by the European Medicines Agency (EMA) guidance (EMA, 2012) as the time from randomization to second objective disease progression, or death from any cause, whichever occurs first. However, continued collection of scans and RECIST assessment after discontinuation from the study is logistically challenging. In the absence of reliable tumor assessments, the end of next-line treatment has been proposed as a surrogate (EMA, 2012). In ovarian cancer patients, however, first subsequent treatment is anticipated to mostly consist of a fixed/ planned number of cycles and end of treatment therefore might not reflect disease progression. There is limited experience with PFS2 in ovarian cancer, although it has been proposed as an endpoint to explore in future studies.[8,71,72]

In this protocol, PFS2 is defined as time from randomization to the start of second subsequent treatment after first documentation of objective progression of disease, or death from any cause. In the setting of ovarian cancer, start of second subsequent therapy was deemed to be the most reliable and unequivocal evidence of second progression.

pCR: Compared to breast cancer, there is relatively little experience with using the rate of pCR as a surrogate endpoint in ovarian cancer. There are also challenges in standardization of pCR assessment, since unlike breast cancer it is difficult to accurately sample the entire tumor bed.

A recent study by Bohm et al, 2015,[67] has tested and validated the prognostic significance of a 3-tier scoring system for grading pathological response to neoadjuvant therapy in patients with high-grade pelvic serous carcinoma. The study included 60 patients in the test cohort and 71 patients in the validation cohort.

This 3-tier scoring system is reproducible, simple and easy to apply, and shows a significant association with clinical outcome when based on pathological assessment of omentum samples.

In this protocol, patients are eligible to enroll prior to receiving neoadjuvant chemotherapy. Since neoadjuvant chemotherapy is one of the stratification factors, randomized groups of patients are expected to receive either chemotherapy alone or chemotherapy + avelumab in a 2:1 ratio. These patients will undergo interval debulking surgery after 3 cycles of chemotherapy. pCR will be assessed using the recently developed pathologic response score.[67,73]

PFS by GCIG criteria will also be assessed in this study incorporating both RECIST 1.1 and CA-125.[68]

1.2.4.4. Chemotherapy Backbone

As outlined in Section 1.2.1, the standard of care in the frontline setting is evolving. Based on the results of the JGOG3016 trial, the JGOG regimen (weekly paclitaxel in combination with Q3W carboplatin) is becoming more widely adopted in some regions. In addition, neoadjuvant chemotherapy is increasingly used. There is no data to suggest that avelumab activity will be impacted by the chemotherapy backbone or whether avelumab is administered before or after debulking surgery. For this reason, the chemotherapy backbone in this study will be selected by the investigator as either the traditional Q3W regimen, or the JGOG3016 regimen incorporating weekly paclitaxel. Patients may be enrolled either before (neoadjuvant) or after (adjuvant) debulking surgery. Either the JGOG3016 or the traditional Q3W chemotherapy may be selected for the adjuvant or neoadjuvant treatment. Neoadjuvant patients will receive 3 cycles of chemotherapy +/- avelumab, followed by interval debulking surgery and the remainder of chemotherapy.

The physician's choice of chemotherapy regimen optimally reflects current clinical practice in the frontline setting. The regimen will be selected prior to randomization, and stratified randomization will be performed to minimize potential imbalance between treatment arms.

1.2.4.5. Stratification Factors

Since the JGOG3016 regimen appears to be superior to the traditional Q3W regimen,[6] the type of chemotherapy backbone will be included as a stratification factor for randomization. Presence or absence of residual disease is the most significant prognostic factor in patients undergoing adjuvant therapy. Even though the adjuvant vs neoadjuvant approaches appear equivalent in terms of OS in high-risk patients,[24] it is unclear whether the same is true in low-risk patients, and whether other endpoints such as PFS or safety are equivalent. Therefore, the following stratification factors were selected:

1. Paclitaxel regimen (Q3W vs QW);
2. Adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection ≤1 cm) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant.

1.2.4.6. Safety Monitoring

Avelumab has not been previously evaluated in combination with platinum doublet chemotherapy. Therefore, close safety monitoring with an enrollment hold after 6 patients are randomized to arm C will be performed as described in Section 3.1.1. Overlapping toxicity is expected to be minimal (Section 1.3).

1.2.5. Rationale for Starting Doses of Avelumab and Chemotherapy (Carboplatin and Paclitaxel)

1.2.5.1. Single Agent Avelumab

In this clinical trial, the dose of avelumab will be 10 mg/kg administered as 1-hour intravenous infusions every 2 weeks (Q2W) as single-agent in the maintenance phase. This dose is the recommended single-agent Phase 2 dose established in the ongoing study EMR 100070-001 (see Section 1.2.2.1 for details). This dose is well tolerated, and signs of antitumor activity, including durable responses, have been observed across various solid tumors, including ovarian cancer. See Section 5.3.1.3 for premedication details.

1.2.5.2. Avelumab in Combination with Chemotherapy

In the chemotherapy phase, due to largely non-overlapping toxicity of the chemotherapy regimen and avelumab, the recommended dose of 10 mg/kg of avelumab will be used as the starting dose in combination with chemotherapy (Arm C). Full doses of pembrolizumab, nivolumab and atezolizumab were successfully combined with platinum doublet chemotherapy.[34-36]

The dose of avelumab in combination with chemotherapy will be 10 mg/kg administered every 3 weeks (Q3W) to avoid dosing of avelumab during the period of maximum bone marrow suppression for patients receiving Q3W chemotherapy. This schedule of avelumab is predicted to achieve therapeutic avelumab levels based upon PK modeling and simulation, resulting in exposures of avelumab needed to achieve >95% PD-L1 target occupancy (Pfizer data on file).

1.2.5.3. Chemotherapy

Chemotherapy regimen will be chosen by the investigator to be one of the following:

Paclitaxel 175 mg/m^2 over 3-hour IV infusion, followed by carboplatin, administered at an area under the curve AUC 5 or AUC 6 as described in Section 5.3.2.2.2 intravenously over 1 hour on Day 1, given every 3 weeks for 6 cycles[3] OR

Paclitaxel 80 mg/m^2 IV over 1-hour on days 1, 8, and 15, and carboplatin administered at an AUC 5 or AUC 6 as described in Section 5.3.2.2.2 intravenously over 1 hour on Day 1, given every 3 weeks for 6 cycles.[5]

1.3. Summary of Benefit/Risk Assessment

Available adverse event and laboratory abnormality data from patients with advanced solid tumors treated with single agent avelumab suggest an acceptable safety profile of the

compound. Most of the observed events were either in line with those expected in patients with advanced solid tumors or with similar class effects of monoclonal antibodies blocking the PD-1/PD-L1 axis. Infusion-related reactions including hypersensitivity and immune related adverse events (irAEs)/autoimmune disorders have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab, including this clinical trial protocol. These include a treatment algorithm and guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with a histamine H1 receptor (H1) blocker and acetaminophen. Avelumab demonstrated clinical activity in heavily pretreated ovarian cancer patients in an expansion cohort of an ongoing Phase 1 study.

The combination of carboplatin with either weekly or Q3W paclitaxel is a standard chemotherapy regimen for previously untreated epithelial ovarian cancer. This regimen has a well characterized toxicity profile. Adverse events frequently seen with this regimen include neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, fatigue, arthralgia, myalgia, and neuropathy. Relevant toxicities of avelumab are largely non-overlapping with chemotherapy except for diarrhea.

Four other checkpoint inhibitors targeting CTLA4, PD1 and PDL1 (ipilimumab, nivolumab, pembrolizumab and atezolizumab) have been combined with platinum doublet chemotherapy demonstrating acceptable safety profiles.[30,33-36] In particular, no increase in hematologic toxicity was observed compared to chemotherapy alone.[30,33]

Close safety monitoring will be performed throughout the study as outlined in Section 3.1.1, including a safety analyses by a E-DMC after 6 patients have been enrolled in each arm, with a hold in enrollment.

Of note, no surgical risk has been identified with immune checkpoint inhibitors;[37] no surgical precautions are mentioned in Keytruda® or Opdivo® product labels.

Thus, the projected benefit/risk of avelumab given as single agent in the maintenance setting following frontline chemotherapy or in combination with carboplatin/paclitaxel is anticipated to be favorable for investigation in this population of newly diagnosed ovarian cancer patients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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 progression free survival (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 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.

CCI

CCI

2.2. Endpoints

2.2.1. Primary Endpoint

- Progression-free survival (PFS) as determined by blinded independent central review (BICR) by RECIST version 1.1

2.2.2. Secondary Endpoints

- Efficacy: Overall survival (OS); PFS by Investigator assessment as well as Objective response (OR); Duration of response (DR);Maintenance PFS by BICR assessment and Investigator assessment; pCR; PFS2; and PFS by GCIG criteria

- Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs)

- Patient-Reported Outcomes: FOSI-18 and EuroQoL5 Dimension (EQ-5D-5L)

- Pharmacokinetics: 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

- Immunogenicity: anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against avelumab

- 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)

2.2.3. Exploratory Endpoints

CCI [redacted]

- CA-125 levels

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

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.

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 (Q3W vs 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:

[redacted]

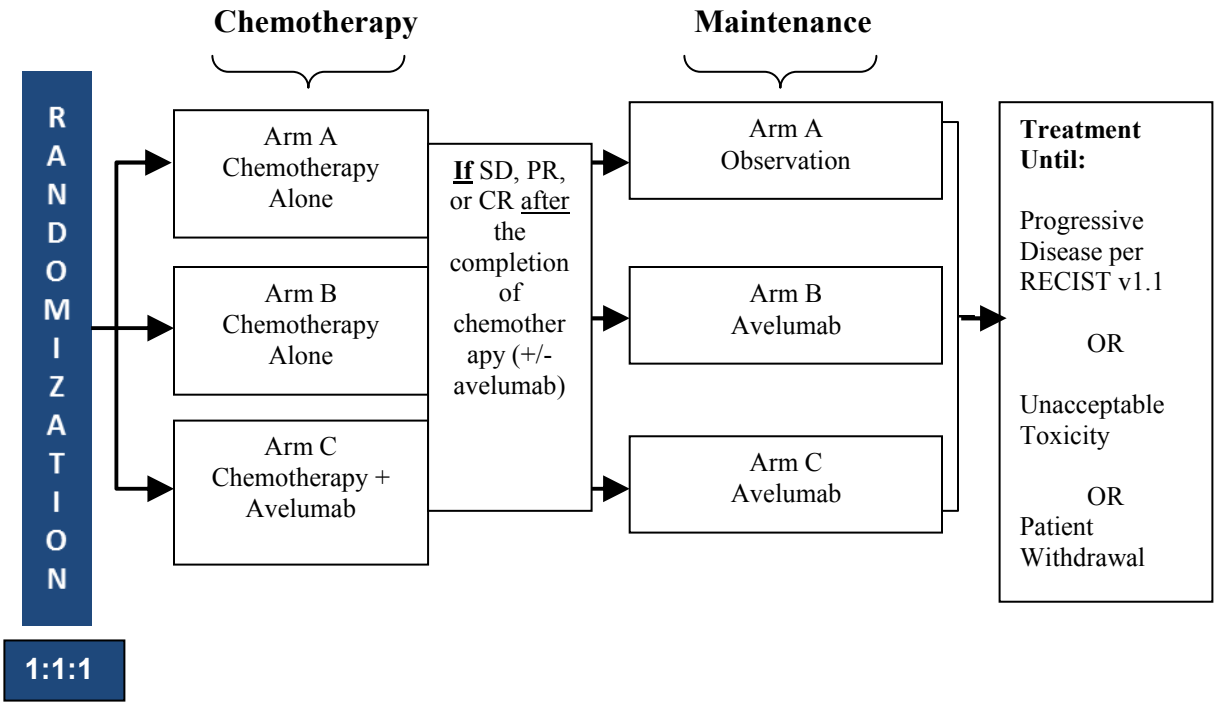
- Arm A: platinum-based chemotherapy alone followed by observation
- Arm B: platinum-based chemotherapy alone followed by avelumab maintenance
- Arm C: avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance.

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 as described in Section 5.1. Crossover between treatment arms will not be permitted.

Intravenous carboplatin-paclitaxel will be used as the chemotherapy backbone, consisting of Q3-week (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, or prior to initiation of neoadjuvant chemotherapy. The latter group will undergo interval debulking surgery 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).

Figure 1. Study Design Schema



3.1.1. Safety Monitoring

The initial evaluation of the safety of the combination of avelumab plus chemotherapy (Arm C) will be performed during the study as follows:

Randomization to all 3 treatment arms will begin at the start of the study. When 6 patients are randomized to the chemotherapy plus avelumab combination arm (Arm C) patient enrollment in all treatment arms will be temporarily held. After each of these 6 patients in Arm C has completed a minimum observation period of 4 weeks, the external data monitoring committee (E-DMC) will evaluate all available safety data. If there are no safety concerns precluding continuation of the study, enrollment for all 3 treatment arms will proceed. Other options may include termination of the combination arm, or enrollment of 6 more patients into Arm C with another temporary enrollment hold. These recommendations will be made at discretion of the E-DMC.

A second safety evaluation will be performed by the E-DMC after a total of 20 patients are enrolled on the chemotherapy plus avelumab combination arm (Arm C) and followed for at least 4 weeks without a patient enrollment hold in any arm. The frequency of subsequent E-DMC meetings for the entire study will be determined by the E-DMC at the time of this second safety evaluation (see Section 9.7).

3.1.2. Study Treatment

The study period includes two treatment phases, the chemotherapy phase and the maintenance phase. For purposes of consistent on-study assessments, 1 study cycle is defined as 3 weeks (21 days) for the chemotherapy phase, and 6 weeks (42 days) for the maintenance phase.

In the **chemotherapy phase** of the study, study drugs will be assigned and given as follows:

Arms A and B: The investigator will have the choice between weekly or Q3W paclitaxel:

Paclitaxel 175 mg/m^2 IV over 3 hours, followed by carboplatin dose AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

OR

- Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8 and 15 plus carboplatin AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

Arm C:

- Chemotherapy (investigator's choice as referenced above) + avelumab 10 mg/kg administered as a 1-hour IV infusion once every 3 weeks for 6 cycles.

The assignment to Arms A and B will be blinded at the time of randomization. In patients who are enrolled prior to neoadjuvant therapy, the first 3 cycles will be administered prior to interval debulking surgery, and the remainder of chemotherapy will be administered after surgery. Upon completion of chemotherapy, patients without evidence of disease progression (SD, PR, or CR) will proceed to the maintenance phase of the study. Disease progression must be confirmed by BICR prior to withdrawal. At this point the assignment to Arms A or B will be unblinded. Maintenance phase should begin within 4 weeks of the last dose of platinum. The first visit of maintenance therapy will be numbered maintenance Cycle 1 Day 1 even if the last chemotherapy cycle was not completed.

In the **maintenance phase** of the study, patients randomized to Arms B or C will receive avelumab 10 mg/kg administered as a 1-hour IV infusion once every 2 weeks.

Patients will receive study treatment until confirmed progressive disease (PD), unacceptable toxicity, or withdrawal of consent, or a maximum duration of 24 months (not including chemotherapy phase), whichever is earliest (see Section 6.5). Patients who discontinue chemotherapy due to unacceptable toxicity will enter maintenance phase and will be on observation (Arm A) or receive avelumab (Arms B and C). Patients who discontinue avelumab due to unacceptable toxicity during the chemotherapy phase may complete chemotherapy and may enter the maintenance with observation only.

Patients without evidence of disease progression by BICR assessment at the time of study treatment discontinuation should continue to undergo tumor assessment until documented radiographic progressive disease by BICR assessment, irrespective of the start of any new anticancer treatment. See Schedule Of Activities (SOA) for details.

Patients who discontinue study treatment (or, if on Arm A maintenance observation, reach End of Treatment/Withdrawal) will be followed every 12 weeks for survival status until death or until study completion, whichever is earlier. Additionally the following data will be collected: surgery and/or new anti-cancer therapies including the date of initiation and discontinuation of each drug.

3.1.2.1. Interval Debulking Surgery After Neoadjuvant Treatment

Patients who are enrolled prior to initiation of neoadjuvant therapy will complete 3 cycles of chemotherapy (with avelumab in Arm C), then treatment will be held, and interval debulking surgery will be performed. Minimal requirements for the interval debulking surgical procedure and guidelines for pathological assessment are provided in Appendix 5. According to institutional practice, upon recovery from surgery, the remainder of chemotherapy (with avelumab in Arm C) should be administered for a maximum of 6 cycles of chemotherapy.

3.1.3. Tumor Assessments

Anti-tumor efficacy will be assessed by radiological tumor assessments conducted at screening and according to the SOA table thereafter, using RECIST v1.1, [redacted] CCI [redacted] (see Appendix 3, [redacted] CCI [redacted] and SOA table).

CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD in the absence of rapid clinical deterioration. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or rising CA-125 levels), and at the time of End of Treatment/Withdrawal (if not done in the previous 12 weeks). Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases.

For patients who undergo interval debulking surgery, an additional tumor assessment should be performed after surgery.

CA-125 will be assessed in a local laboratory every 6 weeks. Rising CA-125 levels alone will not be considered evidence of progression.

3.1.4. Safety

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

4. PATIENT SELECTION

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

4.1. Inclusion Criteria

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

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

1. 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.[38]

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.

4. Availability of an archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 15 slides. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accordance with local institutional practice for tumor biopsies.
5. Eastern Cooperative Group (ECOG) performance status 0-1 (see Appendix 2).
6. Age ≥18 years (or ≥20 years in Japan).
7. Adequate hematological function (ANC ≥1.5 x 10^9/L, Hgb ≥9.0 g/dL, and platelet count ≥100 x 10^9/L).
8. Adequate liver function tests (ALT/AST ≤ 2.5 x ULN, total serum bilirubin level ≤1.5 x ULN).
9. Adequate renal function by estimated creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault method.
10. Estimated life expectancy of at least 12 weeks.
11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

[redacted]

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

13. Patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.

    Patients of non-childbearing potential must meet at least one of the following criteria:

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

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

4.2. Exclusion Criteria

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

1. Non-epithelial tumors or ovarian tumors with low malignant potential (ie, borderline tumors).
2. Mucinous tumors.
3. Patients for whom, in the opinion of the Investigator, there is clinical benefit to administer bevacizumab as a first-line treatment and for whom bevacizumab is approved and available in this setting.
4. Cancer for which intraperitoneal cytotoxic chemotherapy is planned.
5. Prior systemic anti-cancer treatment for EOC, FTC, or PPC.
6. Prior immunotherapy with IL-2, IFN-α, or anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody (including ipilimumab), or any other antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways.
7. Major surgery (other than debulking surgery) for any reason within 4 weeks prior to randomization and/or incomplete recovery from surgery.

8. Known brain, leptomeningeal, or spinal cord metastases.
9. Current or prior use of immunosuppressive medication within 7 days prior to randomization, except the following: intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection); systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; steroids as premedication for hypersensitivity reactions [eg, computed tomography (CT) scan premedication].
10. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents except patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroidism not requiring immunosuppressive treatment.
11. Any of the following in the previous 6 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis or symptomatic pulmonary embolism.
12. Active and clinically significant bacterial, fungal or viral infection, any positive tests for hepatitis B (HBV), hepatitis C (HCV) indicating acute or chronic infection (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive), known history of a positive test for human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness.
13. Administration of a live vaccine within 30 days prior to study entry.
14. Known severe hypersensitivity reactions to monoclonal antibodies, carboplatin, paclitaxel, or other platinum-containing compounds (NCI CTCAE v4.03 Grade ≥3).
15. Persisting NCI CTCAE v4.03 Grade >1 toxicity related to prior therapy.
16. Previous malignant disease other than the target malignancy to be investigated in this trial within the last 5 years with the exception of adequately treated basal or squamous cell carcinoma of the skin, cervical carcinoma *in situ*, lobular carcinoma *in situ* (LCIS), or ductal carcinoma *in situ* (DCIS).
17. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.
18. Participation in other clinical studies involving investigational drug(s) within 4 weeks prior to study randomization and/or during study participation.
19. Other severe/severe acute or chronic medical, including colitis, inflammatory bowel disease, and pneumonitis, or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior) or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

20. Pregnant patients or breastfeeding patients.

21. Patients with bleeding tumors.

4.3. Lifestyle Guidelines

In this study, patients who are of childbearing potential will receive avelumab and/or carboplatin/paclitaxel. The effect of avelumab on reproduction is unknown. Carboplatin and paclitaxel are associated with teratogenic risk.

Those, who, in the opionion of the investigator are sexually active and at risk for pregnancy must agree to use two (2) methods of highly effective contraception throughout the study and continue to do so for 60 days after the last dose of single agent avelumab (Arms B and C). The investigator or his or her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient and her partner from the list of permitted contraception methods (see below) and will confirm the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly according to the Schedule Of Activities and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception method are discontinued or if pregnancy is known or suspected in the patient.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.4. Sponsor's Qualified Medical Personnel

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

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For the purpose of this study, the investigational product is avelumab (MSC0010718C).

The study period includes two treatment phases, the chemotherapy phase and the maintenance phase. In the chemotherapy phase, a cycle is defined as 3 weeks. Due to the biweekly schedule of avelumab in the maintenance phase, 1 study cycle is defined as 6 weeks or 42 days.

For the **chemotherapy phase** of the study, study drugs will be assigned and given as follows:

Arms A and B: The investigator will have the choice between weekly or Q3W paclitaxel:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin dose AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

  OR

- Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8, 15 plus carboplatin AUC 5 or AUC 6 as described in Section 5.3.2.2.2 IV over 1 hour on Day 1 of each 3-week cycle for 6 cycles

Arm C:

- Chemotherapy (as referenced above) + avelumab 10 mg/kg administered as a 1-hour IV infusion once every 3 weeks for 6 cycles.

Upon completion of chemotherapy, patients without evidence of disease progression (SD, PR or CR) will proceed to the maintenance phase of the study Disease progression must be confirmed by BICR prior to withdrawal.

For the **maintenance phase** of the study, patients randomized to Arms B or C will receive avelumab 10 mg/kg administered as a 1-hour IV infusion once every 2 weeks. Patients on Arm A will be on observation only.

BSC for all patients will be provided as deemed appropriate by the treating physician. This could include treatment with antibiotics, analgesic drugs, transfusions and psychosocial and nutritional support, but no active anti-cancer treatment.

Other treatments for progressive disease including chemotherapy and/or palliative radiotherapy will require the patient to be taken off treatment.

All investigational product administration details will be recorded on the case report form (CRF).

5.1. Allocation to Treatment

Once the patient has provided a signed informed consent document (ICD) and has met all inclusion and none of the exclusion criteria, allocation of patients to treatment arms will proceed through the use of an interactive response technology (IRT) system.

The choice of chemotherapy regimen will be made prior to randomization. Allocation of patients will be stratified according to paclitaxel regimen (Q3W vs QW); and adjuvant (complete resection/microscopic disease) vs adjuvant (incomplete resection ≤ 1 cm) vs adjuvant (incomplete resection > 1 cm) vs neoadjuvant. This stratified randomization will be centrally allocated across all centers via the IRT system.

The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the patient number and the date of birth of the patient. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files. IRT will provide a prompt to indicate the patient has completed the chemotherapy phase and is proceeding to the maintenance phase of the study. The site personnel (study coordinator or specified designee) will then be provided with the Treatment Group assignment.

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

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

Qualified patients will be randomized in a 1:1:1 ratio as follows:

	Chemotherapy Phase	Maintenance Phase
Arm A	Chemotherapy Alone	Observation
Arm B	Chemotherapy Alone	Avelumab
Arm C	Avelumab + Chemotherapy	Avelumab

The assignment to Arms A vs B will be blinded for the patient, investigator, and Sponsor at the time of randomization. Upon completion of chemotherapy, patients without evidence of disease progression by BICR assessment (SD, PR, or CR) will proceed to the maintenance phase of the study. At this point, the assignment to Arms A vs B will be unblinded.

5.2. Patient Compliance

In this trial, patients will receive trial treatment (ie, chemotherapy and avelumab) at the investigational site. Well-trained medical staff will monitor and perform the trial drug administration. The information of each trial drug administration including the date, time, and dose of trial drug will be recorded on the eCRF. The Investigator will make sure that the information entered into the eCRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

Noncompliance is defined as a patient missing > 1 infusion of trial treatment for non-medical reasons (see Section 6.5). If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for nonmedical reasons, the criteria of insufficient compliance are met as well.

5.3. Investigational Product Supplies

5.3.1. Avelumab

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

5.3.1.1. Avelumab Dosage Form and Packaging

Avelumab is a sterile, clear, and colorless solution intended for IV administration. Avelumab is formulated as a 20 mg/mL solution and will be supplied by the Sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal.

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

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

5.3.1.2. Avelumab Preparation

See the dosing and administration instruction (DAI) section of the Investigational Product Manual (IP Manual) for instructions in how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

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

Avelumab will be administered at the investigational site.

The contents of the avelumab vials are sterile and non-pyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard clean-up procedures for biologic products.

For administration in this trial, avelumab must be diluted with 0.9% sodium chloride (normal saline solution). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the DAI section of the IP Manual. Must use tubing with in line, low protein binding 0.2 micron filter made of polyether sulfone (PES) during administration.

The dose amount required to prepare the avelumab infusion solution will be based on the patient's weight in kilograms (kg). All patients should be weighed within 3 days prior to dosing for each dose to ensure they did not experience either a weight loss or gain of >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

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

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

5.3.1.3. Avelumab Administration

All study treatments will be administered at the investigational site on an outpatient basis as described in the DAI section of the IP Manual.

Avelumab 10 mg/kg will be administered on Day 1 of each 3-week study cycle during the chemotherapy phase and on Days 1, 15, and 29 of each 6-week study cycle during the maintenance phase and after all procedures/assessments have been completed as described in the SOA table. Avelumab may be administered up to 3 days before or after the scheduled day of administration of each cycle due to administrative reasons.

Avelumab will be administered as a 1-hour IV infusion. In order to mitigate infusion-related reactions, a premedication regimen of diphenhydramine 25 to 50 mg IV or oral equivalent and acetaminophen/paracetamol 500 to 650 mg IV or oral equivalent (as per local practice) is mandatory approximately 30 to 60 minutes prior to each dose of avelumab. This may be modified based on local treatment standards and guidelines, as appropriate.

For patients on Arm C, on visits when both chemotherapy and avelumab are infused (Days 1 and 22) of each 6-week cycle, avelumab will be infused *after* chemotherapy. If premedication was administered prior to chemotherapy, the decision whether to repeat pre-medication prior to avelumab is at the discretion of the investigator depending on the elapsed time and the half-life of corresponding premedication agent. The line should be flushed, according to local practice, between infusions, and a new administration set should be used for avelumab.

Sites should make every effort to target the timing of avelumab infusion to be as close to 1 hour as possible. However, given the variability of infusion pumps from site to site, time windows of minus 10 minutes and plus 20 minutes is permitted (ie, infusion time is 50-80 minutes). The exact duration of infusion should be recorded in both source documents and CRFs. Possible modifications of the infusion rate for the management of infusion-related reactions are described in Section 5.3.5.1.

Patients will receive trial treatment until confirmed progressive disease (PD) per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or if any criterion for withdrawal from the trial or trial treatment is fulfilled.

Patients who temporarily stop the study treatments due to AE may resume treatments upon recovery as described in the relevant protocol section (study drug dose delay or discontinuation for drug related toxicities, including irAEs).

5.3.1.3.1. Treatment After Initial Evidence of Radiologic Disease Progression (Only for Patients in the Maintenance Phase)

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

If radiologic imaging shows disease progression, tumor assessment should be repeated ≥4 weeks later in order to confirm the observation. Avelumab may be continued at the Investigator's discretion while awaiting radiologic confirmation of disease progression.

Before continuation of treatment, the patient must provide new consent and be informed that in order to continue receiving the investigational products on study, the patient may be foregoing approved therapy with possible clinical benefit(s).

Patients may receive avelumab while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease by radiographic imaging.
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.
- If repeat imaging no longer shows PD but rather CR, PR, or SD compared to the initial scan, treatment may be continued/resumed. In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target as well as non-target lesions (refer to the imaging charter).
- If the repeat imaging confirms PD, patients should be discontinued from study treatment. However, according to the investigator's clinical judgment and after discussion between the investigator and the sponsor's medical monitor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with avelumab. The investigator's judgment should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.
- Patients in the maintenance phase who stop avelumab treatment, and then experience radiologic disease progression assessed by BICR thereafter, will be eligible for re-treatment with avelumab at the discretion of the investigator and after discussion with

the sponsor's medical monitor if 1) no cancer treatment was administered other than BSC since the last dose of avelumab, 2) the patient does not meet the safety withdrawal criteria, 3) the patient meets all initial eligibility criteria except for exclusion criteria #4 and #5, and 4) the trial is still open.

5.3.2. Paclitaxel and Carboplatin

Paclitaxel and carboplatin to be administered during this study will be branded or generic product available in the local region. Note that nanoparticle protein bound paclitaxel (nab-paclitaxel, Abraxane®) may NOT be substituted for the cremophor formulation of paclitaxel. Paclitaxel and carboplatin are commercially available, and are to be stored, prepared, and administered according to locally approved product labeling.

5.3.2.1. Premedication for Chemotherapy Administration

Premedication to ameliorate the toxicities associated with the chemotherapy are to be administered according to the local product label or institutional guidelines.

5.3.2.1.1. Paclitaxel

Premedication regimens that are standard for the institution or region will be used. Premedication will be supplied by the site. The effect of steroid premedication in Arm C chemotherapy phase on the activity of avelumab is unknown (see Section 5.6.4).

5.3.2.1.2. Carboplatin

Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with anti-emetics. Because anti-emetics are given as part of the paclitaxel regimen, extra doses as premedication are not necessary, although additional doses may be required if the patient develops emesis. Premedication according to institutional guidelines should be used if paclitaxel has been discontinued. No pre- or post-treatment hydration or forced diuresis is required.

5.3.2.2. Chemotherapy Regimen and Starting Doses

In the absence of progressive disease, patients will receive paclitaxel and carboplatin treatment for 6 cycles during the chemotherapy phase of the study. Dose reduction for toxicity is allowed (see Section 5.3.3).

All patients should be weighed within 3 days prior to dosing for every cycle to ensure they did not experience either a weight loss or gain of >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the chemotherapy doses can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

5.3.2.2.1. Paclitaxel

Following pre-medication, paclitaxel is administered as the first drug when chemotherapy is administered. For this study, the investigator has a choice between weekly and Q3W paclitaxel regimen:

- Paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 of each 3-week cycle

  OR

- Paclitaxel 80 mg/m^2 IV over 1 hour on Days 1, 8 and 15 of each 3-week cycle

5.3.2.2.2. Carboplatin

Carboplatin is administered over 1 hour, beginning 60 minutes after completion of the paclitaxel infusion on Day 1 of each 3-week study cycle.

The carboplatin dose should be calculated according to the Calvert[39] formula as follows:

Carboplatin dose = Target AUC x (GFR + 25).

Maximum Carboplatin Dose (mg) = target AUC (mg·min/mL) x (150 mL/min)

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

- For a target AUC = 6, the maximum dose is 6 x 150 = 900 mg
- For a target AUC = 5, the maximum dose is 5 x 150 = 750 mg
- For a target AUC = 4, the maximum dose is 4 x 150 = 600 mg

For the purpose of this protocol the GFR is considered equivalent to the creatinine clearance. The exact dose of carboplatin therefore depends on the GFR and the method of calculating the GFR will also affect the carboplatin dose. The GFR can be calculated using a variety of different formulae (see below) and should be calculated as per local practice. Where the carboplatin dose is based on a GFR measured by isotopic clearance or calculated using the Wright formula, the target AUC is one unit lower than that based on the GFR calculated by using the Cockroft-Gault or Jellife formula, or the GFR measured by 24 hour urine collection. This is summarized below. The reason for this is that the GFR calculated using the Cockroft-Gault or Jeliffe formula has been shown to significantly underestimate the GFR as measured isotopically, whereas the GFR as calculated by the Wright formula does not appear to do so.

- If using Cockroft-Gault/Jellife formula, use AUC6
- If using the Wright formula, use AUC5

- If using isotopic method (51Cr EDTA), use AUC5
- If using 24hr urine, use AUC6.

GFR Limitations

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

If, therefore, prior to Cycle 1, the serum creatinine is low (≤ 0.6mg/mL or ≤ 53μmol/L) or there is evidence of some impairment of renal function (estimated creatinine clearance is < 60 mL/minute), then a formal measurement of the GFR is required, using either a 24 hour urine collection or an isotopic clearance. If the isotopic clearance is measured then the value uncorrected for body surface area (BSA) should be used in dose calculations.

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

5.3.3. Recommended Dose Modifications

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

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

Table 5. Dose Modification Levels for Paclitaxel and Carboplatin

Drug	Starting Dose	Dose Level -1	Dose Level -2
Paclitaxel Weekly	80 mg/m^2	60 mg/m^2	45 mg/m^2
Paclitaxel Q3W	175 mg/m^2	135 mg/m^2	110 mg/m^2
Carboplatin	AUC 6	AUC 5	AUC 4
Carboplatin	AUC 5	AUC 4	AUC 3

In order to maintain the dose-intensity and cumulative dose-delivery of carboplatin and paclitaxel chemotherapy, reasonable efforts should be made to minimize dose reduction and treatment delays. Patients whose treatment is delayed because of adverse events should be evaluated at weekly intervals (or less) until adequate recovery has occurred. Intrapatient dose escalations are not permitted (including dose re-escalation after a dose reduction).

Dose levels should be adjusted independently for each drug. Patients who do not tolerate two carboplatin and/or paclitaxel dose reductions should discontinue treatment with trial chemotherapy.

5.3.3.1. Dose Modifications for Avelumab as Single Agent

For avelumab, no dose reductions are permitted in this study, but doses may be omitted based on persisting toxicity.

Any adverse event suspected to be immune related should be managed according to the guidance for management of irAEs (see Table 7).

5.3.4. Guidelines for Avelumab Toxicity Management

5.3.4.1. Adverse Drug Reaction Requiring Avelumab Discontinuation or Delays

The following adverse reactions (ADRs) require permanent treatment discontinuation of avelumab:

Any Grade 4 ADRs require avelumab treatment discontinuation except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any Grade 3 ADRs require avelumab treatment discontinuation except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to Grade ≤ 1

- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to trial treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management

- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

- Change in Eastern Cooperative Oncology Group Performance Status (ECOG PS) to ≥ 3 that resolves to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of trial drug administration).

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 within 2 weeks treatment may continue.

- If a Grade 2 ADR does not resolve to Grade ≤ 1 within 2 weeks, avelumab should be held. If after another 2 weeks the event has not resolved to Grade 1, the patient should permanently discontinue treatment with an avelumab (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same patient, treatment with avelumab has to be permanently discontinued.

Avelumab infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), tumor lysis syndrome, and irAEs should be handled according to guidelines in Sections 5.3.5.1, 5.3.5.2 and 5.3.5.3.

5.3.5. Special Precautions for Avelumab Administration

In order to mitigate avelumab infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral). This may be modified based on local treatment standards and guidelines, as appropriate.

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

Infusion of avelumab will be stopped in case of Grade ≥ 2 infusion-related, allergic, or anaphylactic reactions. Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. If an allergic reaction occurs, the patient must be treated according to the best available medical practice. The emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Treatment recommendations for the management of infusion-related reactions, severe hypersensitivity reactions, tumor lysis syndrome, and immune-related AEs are outlined in Sections 5.3.5.1, 5.3.5.2, 5.3.5.3 and 5.3.5.4, respectively.

5.3.5.1. Management of Avelumab Infusion-Related Reaction

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 6.

Table 6. Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening. The total infusion time for avelumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop avelumab infusion. Resume infusion at 50% of previous rate as soon as infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the avelumab infusion immediately and disconnect bag infusion tubing from the patient. Patients have to be withdrawn immediately form avelumab treatment and must not receive any further avelumab treatment.

IV=intravenous, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% due to an infusion related reaction, it must remain so for all subsequent infusions.

Additional Modifications for Patients with Grade 2 Infusion-Related Reactions: If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in Table 6 (including reducing the infusion rate by 50%), the Investigator may consider treatment with corticosteroids, and the infusion should not be resumed. At the next dose, the Investigator may consider the addition of H2 blocker antihistamines (eg, famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids are NOT permitted.

5.3.5.2. Avelumab: Severe Hypersensitivity Reactions

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Patients should be instructed to report any delayed reactions to the Investigator immediately.

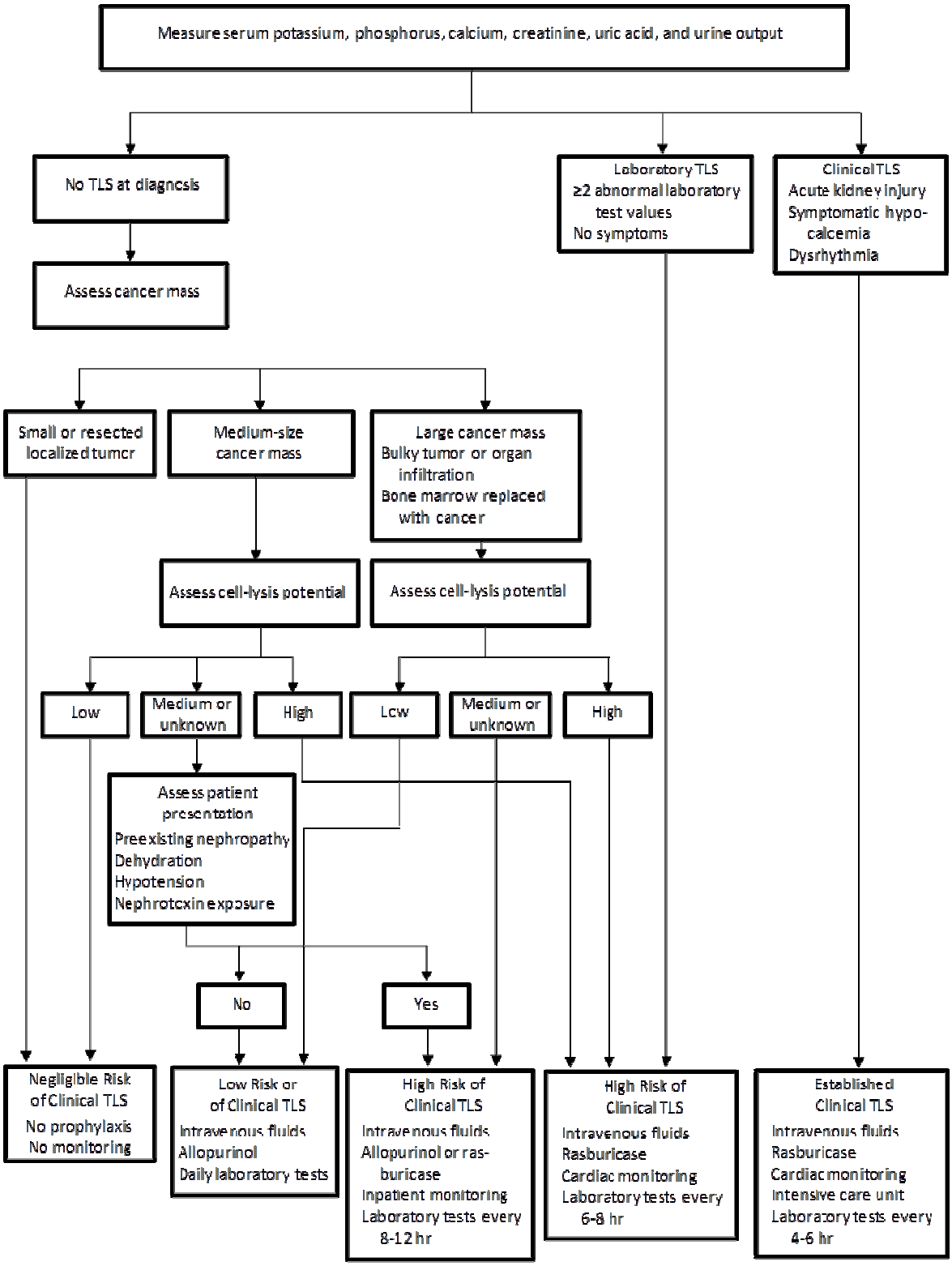
Symptoms include impaired airway, decreased oxygen saturation (<92%), confusion, lethargy, hypotension, pale or clammy skin, and cyanosis. These symptoms can be managed with epinephrine injection and dexamethasone. Patients should be placed on monitor immediately, and the intensive care unit (ICU) should be alerted for possible transfer if required.

For prophylaxis of flu like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to patients at the discretion of the investigator.

5.3.5.3. Avelumab: Tumor Lysis Syndrome

Tumor lysis syndrome should be treated per the local guidelines and the management algorithm published by Howard et al.[40]

Figure 2. Assessment and Initial Management of Tumor Lysis Syndrome



TLS=tumor lysis syndrome.

5.3.5.4. Avelumab: Immune-Related Adverse Events

Because inhibition of PD-L1 stimulates the immune system, avelumab may cause toxicity by increasing the immune response, leading to inflammatory reactions collectively referred to as immune-related adverse events (irAEs).[69]

Immune-related adverse events described with this class of drugs include drugs include pneumonitis, colitis, hepatitis, endocrinopathies including thyroid disorders (hyperthyroidism, hypothyroidism, thyroiditis), adrenal insufficiency, hypophysitis, and diabetes mellitus or hyperglycemia, rash, nephritis and renal dysfunction, encephalitis, eye disorders (including uveitis, iritis), and other immune-mediated reactions including myositis and myocarditis.

Any adverse event which may have an underlying immune-mediated mechanism including those described above, and without other confirmed etiologies, should be considered immune-related and managed according to guidelines described in this section.

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

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

For patients receiving avelumab alone or in combination with chemotherapy, any event suspected to be immune-related should be managed according to the guidance for management of irAEs in this section and Table 7.

For patients receiving avelumab in combination with chemotherapy (Arm C), in case of a potential irAE, besides the management related to avelumab therapy, carboplatin/paclitaxel doses may also be modified or interrupted based on the guidance provided for carboplatin/paclitaxel toxicity management in Section 5.3.6.5, product labeling, and institutional guidelines according to investigator's best medical judgment.

In cases where use of corticosteroids or other immunosuppressants is required per guidance for management of avelumab irAEs, chemotherapy may also be placed on hold until the irAE resolves to Grade 1 based on investigator's medical judgment and after discussion with the Sponsor.

Table 7. Avelumab: Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: <4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (eg, loperamide)	Close monitoring for worsening symptoms Educate patient to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists >5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists >3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methlyprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists >3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

[redacted]

Table 7. Avelumab: Management of Immune-Related Adverse Events

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grades 1 to 2 Covering ≤30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists >1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grades 3 to 4
Grades 3 to 4 Covering >30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4

Table 7. Avelumab: Management of Immune-Related Adverse Events

Grade of Pneumonitis (NCI-CTCAE v4.03)	Management	Follow-up
Grades 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grades 2 or 3 to 4
Grade 2 AST or ALT >3.0 to ≤5 x ULN and / or total bilirubin >1.5 to ≤3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist >5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy

[redacted]

Table 7. Avelumab: Management of Immune-Related Adverse Events

Grades 3 to 4 AST or ALT >5 x ULN and / or total bilirubin >3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in >3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH <0.5 x LLN, or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab/pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks/MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

Table 7. Avelumab: Management of Immune-Related Adverse Events

ADL=activities of daily living, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CT=computed tomography; irAE=immune related adverse event, IV=intravenous, LFT=liver function test, LLN=lower limit of normal, MRI=magnetic resonance imaging, NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, anti-inflammatory drugs, T4=free thyroxine, TSH=thyroid-stimulating hormone, ULN=upper limit of normal

5.3.6. Guidelines for Chemotherapy Toxicity Management

Dose modification (dose delays and dose change) for carboplatin/paclitaxel due to ADRs should be made in accordance with the guidance provided below, product labeling and institutional guidelines. Starting doses for carboplatin and paclitaxel and dose reduction levels are described in Table 5.

5.3.6.1. General Guidelines for Hematologic Toxicity

Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white blood cell (WBC) count.

Day 1 of each cycle of cytotoxic chemotherapy will not be administered until the ANC is ≥1,000 cells/μL and the platelet count is ≥75,000/μL. All treatment (including avelumab on Arm C) will be delayed until these levels are achieved. Chemotherapy can be delayed for a maximum of 3 weeks. Patients who fail to recover adequate ANC despite a 3-week delay will no longer receive chemotherapy.

Additionally, for patients on dose-dense chemotherapy, the Day 8 and Day 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/μL and the platelet count is at least 50,000/μL. If not given, these doses are to be omitted and not made up.

5.3.6.2. Use of Hematopoietic Growth Factors

It is anticipated that myelosuppression may be a significant side effect of chemotherapy. Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that that NCCN and/or American Society of Clinical Oncology (ASCO) guidelines[41] be consulted). Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

5.3.6.3. Modifications for Hematologic Toxicities

There will be no paclitaxel dose reductions based on hematologic toxicity, however, paclitaxel dose omissions may be recommended on the weekly regimen as described in Table 9.

Initial occurrence of dose-limiting neutropenia or dose-limiting thrombocytopenia will be managed according to Table 8 and Table 9.

- Dose-limiting neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia (as defined within the CTCAE), prolonged Grade 4 neutropenia persisting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia,

ANC < 1000 cells/μl on Day 1, or omission of Day 8 or Day 15 paclitaxel because of neutropenia.

- Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/μl) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/μl), delay of treatment on Day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of <75,000/μl on day 1, or inability to give Day 8 or Day 15 paclitaxel on the dose-dense regimen due to thrombocytopenia. There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

Table 8. Modification Instructions for Hematologic Toxicity: Q3W Chemotherapy Regimen

DLT ANC	DLT PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin one AUC unit	Add G-CSF and maintain all current drug doses	Discontinue chemotherapy
Yes	Yes	Reduce carboplatin one AUC unit	Add G-CSF and maintain all current drug doses	Discontinue chemotherapy
No	Yes	Reduce carboplatin one AUC unit	Reduce carboplatin one AUC unit	Discontinue chemotherapy

Table 9. Modification Instructions for Hematologic Toxicity: Weekly Chemotherapy Regimen

DLT ANC	DLT PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel	Reduce caboplatin one AUC unit, and give G-CSF after day 8 paclitaxel. Fourth occurrence: Discontinue chemotherapy.
Yes	Yes	Reduce carboplatin one AUC unit	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel, and reduce carboplatin one AUC unit	Discontinue chemotherapy
No	Yes	Reduce carboplatin one AUC unit	Reduce carboplatin one AUC unit	Discontinue chemotherapy

5.3.6.4. Dose Modifications and Delays of Chemotherapy: Other Non-Hematologic Toxicities and Laboratory Abnormalities

5.3.6.4.1. Renal Toxicity

The combination of carboplatin and paclitaxel, with or without avelumab, is not directly expected to cause renal toxicity. There are, therefore, no specific dose modifications for renal toxicity.

The administered dose of carboplatin must however be recalculated each cycle in any patient who develops renal insufficiency defined by serum creatinine greater than 1.5 times the ULN.

5.3.6.4.2. Hepatic Toxicity

Hepatic toxicity is not expected as a direct complication of chemotherapy; however, in the event of Grade 3 (or greater) elevation in AST, ALT, alkaline phosphatase, or total bilirubin, paclitaxel should be reduced by 1 dose level and chemotherapy should be delayed until recovered to Grade 1. For patients receiving chemotherapy in combination with avelumab, any event potentially immune-related should be managed according to the guidance described in Section 5.3.5.4 and Table 7 for avelumab irAEs. In cases where use of corticosteroids or other immunosuppressants is required per guidance for management of avelumab irAEs, chemotherapy may also be placed on hold until the irAE resolves to Grade 1 based on investigator's medical judgment and after discussion with the Sponsor.

5.3.6.4.3. Neuropathy

Grade ≥ 2 sensory or motor neuropathy requires paclitaxel treatment to be interrupted until neuropathy has resolved to a maximum of Grade 1. Upon recovery, paclitaxel should be reduced by 1 dose level. If this requires a delay of more than 3 weeks, then paclitaxel should be omitted from subsequent cycles and treatment continued with single agent carboplatin at the same AUC used in combination with paclitaxel.

Grade ≥ 3 sensory or motor neuropathy requires paclitaxel to be omitted from subsequent cycles, and treatment continued with single-agent carboplatin at the same dose as previously used.

5.3.6.4.4. Mucositis

For Grade ≥ 3 mucositis, chemotherapy should be delayed until the mucositis has resolved to Grade ≤ 1. Paclitaxel may be reduced by one dose level in subsequent cycles based on investigator's medical judgment.

5.3.6.4.5. Hypersensitivity to Paclitaxel

A hypersensitivity reaction to paclitaxel is not a dose-limiting toxicity. The acute management should occur as per local practice.

If a hypersensitivity reaction occurs, then patients may be retreated with paclitaxel at full dose according to local protocols. This is likely to include increased prophylactic medications and/or a slowing of the initial infusion rate with a gradual increase in rate in the absence of further hypersensitivity reactions.

Emergency resuscitation equipment and personnel should be available during the period of re-challenge.

If the re-challenge occurs within 72 hours of the original intended dose and a negligible quantity, ie, ≤ 50 mL, of the original dose was administered, then re-administer the full dose. If a substantial proportion has been given then the balance of the full original dose should be administered.

If the re-challenge is being considered more than 72 hours after the original intended dose then a full blood count should be taken to check suitability.

In the case of recurrent hypersensitivity reactions, despite adequate premedication, paclitaxel may be discontinued at the discretion of the treating physician, and the patient may continue on treatment with single-agent carboplatin ± avelumab.

5.3.6.4.6. Hypersensitivity to Carboplatin

If there is a hypersensitivity reaction to carboplatin, then this should be managed as per local institutional protocols.

In the case of recurrent hypersensitivity reactions, despite adequate premedication, carboplatin may be discontinued at the discretion of the treating physician, and the patient may continue on treatment with single agent paclitaxel ± avelumab.

5.3.6.4.7. Other Toxicities of Chemotherapy

For patients on chemotherapy alone (Arms A and B), there are no dose modifications planned for alopecia, nausea, diarrhea, or constipation. These side effects should be treated with supportive medical therapy. Non-steroidal anti-inflammatory agents may be used prophylactically, or symptomatically, as per local practice for the treatment of paclitaxel-induced arthromyalgia.

For any other adverse event of NCI CTCAE v4.03 Grade 4 severity considered at least possibly related to chemotherapy treatment, the patient should be discontinued from chemotherapy treatment.

For any other adverse event of NCI CTCAE v4.03 Grade 3 severity considered at least possibly related to chenotherapy treatment, treatment should be withheld until recovery to Grade ≤1 and subsequent treatment should be reduced by one dose level (see Table 5).

5.3.6.5. Dose Modifications for Avelumab in Combination With Chemotherapy (Chemotherapy Phase – Arm C)

For avelumab, no dose reductions are permitted in this study, but doses may be omitted based on persisting toxicity.

For patients on Arm C (avelumab in combination with chemotherapy), chemotherapy dose modifications as well as infusion omissions/delays for chemotherapy and/or avelumab may occur independently according to the guidance provided below and investigator's medical judgment and will be reported in the CRF.

Toxicities of the carboplatin paclitaxel combination and avelumab are generally non-overlapping. For patients receiving avelumab either as a single agent or in combination with chemotherapy, any adverse event suspected to be immune related should be managed according to the guidance for management of irAEs (see Table 7). For Grade ≥ 3 potentially immune-related toxicities or where use of corticosteroids or other immunosuppressant is required per guidance for management of avelumab irAEs, chemotherapy may also be placed on hold until the irAE resolves to Grade 1 based on investigator's medical judgment and after discussion with the Sponsor.

Refer to Table 10 for guidance on management of toxicities in the combination treatment arm (Arm C) during the chemotherapy phase.

For any other adverse event not covered in Table 10 below, see Section 5.3.4 for avelumab toxicity management and Section 5.3.6.4.7 for chemotherapy toxicity management.

Table 10. Avelumab in Combination with Chemotherapy (Arm C) Toxicity Management

Toxicity	Treatment Modification for Chemothrerapy	Treatment Modification for Avelumab
Hematologic toxicity	See Section 5.3.6.3.	Delay until ANC is ≥1,000 cells/μL and the platelet count is ≥75,000/μL.
Adverse events with potential immune-related etiology (see Section 5.3.5.4) such as Colitis/diarrhea, Hepatic/Liver test abnormalities, Rash, Pneumonitis, Endocrinopathy, Nephritis/Renal dysfunction	Continue chemotherapy for G1/G2 events. Chemotherapy may be placed on hold for events Grade ≥ 3 or events requiring corticosteroids / immunosuppressant, until the event resolves to Grade ≤ 1 based on investigator's medical judgment and after discussion with the Sponsor.	See Section 5.3.5.4 and Table 7

Table 10. Avelumab in Combination with Chemotherapy (Arm C) Toxicity Management

Toxicity	Treatment Modification for Chemothrerapy	Treatment Modification for Avelumab
Neuropathy (sensory or motor)	Grade 2: Delay paclitaxel until event resolves to Grade ≤ 1 and then resume paclitaxel at 1 reduced dose level. If required delay > 3 weeks, paclitaxel should be permanently discontinued and treatment continued with single agent carboplatin. Grade ≥ 3: Permanently discontinue paclitaxel and treatment continued with single agent carboplatin (see Section 5.3.6.4.3).	Continue avelumab therapy for G1/G2 events. Avelumab may be placed on hold for events Grade ≥ 3, until the event resolves to Grade ≤ 1 based on investigator's medical judgment and after discussion with the Sponsor.
Mucositis	Grade ≥ 3: Delay chemotherapy until event resolves to Grade ≤ 1. Paclitaxel may be reduced by one dose level in subsequent cycles based on investigator's medical judgment See Section 5.3.6.4.4.	Continue avelumab therapy for G1/G2 events. Avelumab may be placed on hold for events Grade ≥ 3, until the event resolves to Grade ≤ 1 based on investigator's medical judgment and after discussion with the Sponsor.
Hypersensitivity	Managed according to the local guidelines. In case of Grade ≥3 hypersensitivity reaction to paclitaxel or carboplatin, avelumab treatment should be postponed until symptoms resolve. If symptoms do not resolve within 72 hours, avelumab dose should be skipped See Section 5.3.6.	See Section 5.3.5.1 and Table 6.

5.4. Investigational Product Storage

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

Investigational product should be stored in its original container and in accordance with the label. See the IP Manual for storage conditions of the product.

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

Storage conditions for avelumab stated in the single reference safety document (SRSD) (Investigator's Brochure [IB]) will be superseded by the storage conditions stated in the labeling.

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

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

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

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

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

5.5. Investigational Product Accountability

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

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

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

At the end of the trial, or at appropriate points during the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. If drug destruction is not permitted locally, Pfizer should be contacted for further directions.

5.5.1. Destruction of Investigational Product Supplies

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

5.6. Concomitant Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, except for administration of inactivated vaccines (for example, inactivated influenza vaccine).

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy may be required. The Investigator should consult with the Sponsor about individual cases. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the patient.

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

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications and non-drug supportive interventions should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (ie, antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.6.1. Concomitant Radiotherapy

Local radiotherapy (limited field) of isolated lesions with palliative intent is acceptable (eg, bleeding, pain, compression), and allowed throughout the study (starting from the screening through end of treatment) if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of localized pain. If palliative radiotherapy is needed to control pain, the site(s) of disease causing pain should also be present at baseline; otherwise, painful lesions requiring radiotherapy will be considered as a sign of disease progression. The Medical Monitor should be consulted prior to starting radiotherapy and prior to restarting study treatment after the end of radiotherapy.

5.6.2. Supportive Care Guidelines

Palliative and supportive care for disease-related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

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

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

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

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 7 Avelumab Management of Immune related Adverse Events.

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

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

5.6.3. Concomitant Surgery

5.6.3.1. Interval Debulking

Patients who are enrolled prior to initiation of neoadjuvant therapy will complete 3 cycles of chemotherapy (with avelumab in Arm C), treatment will be held, and patients will proceed to have interval debulking surgery. For those patients who receive the weekly paclitaxel regimen, the pre-surgery, D15 paclitaxel dose may be omitted at the investigator's discretion. Upon recovery from surgery, the remaining duration of chemotherapy (with avelumab in Arm C) should be administered according to local institutional practice. A histological assessment of response to neoadjuvant chemotherapy must be performed on the surgical specimen and will be recorded in the CRF (see Appendix 5).

Patients who cannot undergo planned interval debulking surgery are allowed to continue study treatment provided no disease progression is documented.

5.6.3.2. Other Surgery

If a major surgery or an interventional procedure (eg, endoscopy) is required, then treatment with avelumab must be interrupted. Patients may resume avelumab 2-3 weeks after major surgery, assuming the wound has completely healed and there are no wound healing complications (eg, delayed healing, wound infection or fistula).

In case of a minor surgical procedure, treatment with avelumab does not need to be delayed.

5.6.4. Other Prohibited Concomitant Medications and Treatments

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

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than carboplatin/paclitaxel and avelumab.
- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.6.1).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of irAEs (see Table 7 and below Clarification about Steroid Use).
- Medications or vaccinations specifically prohibited in the exclusion criteria are also not allowed during the active treatment period, however, the administration of inactivated vaccines (eg, influenza vaccine) is allowed during the study.
- Herbal remedies or vitamins used as anticancer treatments.

- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (eg, hypericin).
- For patients on avelumab, acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

Clarifications About Steroid Use with Avelumab: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[42,43] Furthermore, as with all immunotherapies intended to augment cell mediated immunity, there is a risk that concomitant immunosuppressives such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short term use of steroids may be employed without compromising clinical outcomes.[44] Therefore, the use of steroids during this trial is restricted as follows:

- Premedication: steroid inclusion in the premedication regimen for paclitaxel or carboplatin is allowed in all study arms.
- Therapeutic use: for the treatment of infusion-related reactions and short term treatment of irAEs, steroids are permitted according to the modalities indicated in Table 7 Avelumab Management of Immune-Related Adverse Events, they are also permitted for any other medical condition requiring short-term use of steroids.
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.

5.6.4.1. Potential Drug-Drug Interactions

The pharmacokinetics carboplatin and paclitaxel when co-administered have been evaluated in various studies. No drug-drug interactions were observed between carboplatin and paclitaxel.[45,46] Addtionally, no drug-drug interactions are expected between chemotherapy and a monoclonal antibodies based upon different elimination pathways (ie metabolism vs catabolism). Previous studies where chemotherapy, including paclitaxel/carbotaxol combinations, was administered with large molecules (eg, figitimumab, bevacizumab) did not show any clinically significant PK drug-drug interactions.[47,48,49]

5.6.4.1.1. Paclitaxel

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

5.6.4.1.2. Carboplatin

There are no anticipated drug-drug interactions or precautions for carboplatin.

5.6.4.1.3. Avelumab

There are no anticipated drug-drug interactions or precautions for avelumab.

6. STUDY PROCEDURES

All patients must sign an informed consent prior to any study-specific procedures.

6.1. Screening

To allow for additional flexibility in scheduling patient visit and procedures, Screening and Cycle 1 Day 1 procedures may be completed on the same day (see SOA table). However, screening assessments for *eligibility* MUST have already been completed before the patient is randomized.

Following informed consent, patients who are screened for treatment and complete screening assessments will subsequently be randomized to 1 of the 3 treatment arms for the study. Treatment must start within 7 days after randomization.

6.1.1. Tumor Biopsies

Provision of tumor biospecimen will be required as follows:

1. Archival tumor biospecimen: A mandatory archival FFPE tumor tissue block from the initial tumor specimen (debulking surgery or core biopsy for patients planning to undergo neoadjuvant therapy) must be provided from all patients prior to randomization. If an FFPE tissue block cannot be provided, 15 unstained slides (10 minimum) will be acceptable. If archived FFPE tissue is not available, a de novo (ie, fresh) tumor sample must be obtained in accordance with local institutional practice for tumor biopsies.
2. On-study FFPE surgical specimen (for neoadjuvant patients only):
    a. for pCR assesment: The H&E slides used for the local assessment of pCR performed according to the guidelines described in Appendix 5 should be provided (i.e., from each of the 4-6 blocks examined for assessment of pCR), The slides will be digitally imaged and returned to the site;

b. for biomarker assessments: The FFPE tumor tissue block that was selected for local pCR scoring per the guidelines described in Appendix 5 should be provided. . If the block cannot be provided due to local regulations, 15 unstained slides (10 minimum) will be acceptable.

3. End of Treatment/Withdrawal Tumor Biospecimen: A *de novo* tumor sample (ie, fresh biopsy) should be collected at End of Treatment/Withdrawal visit unless clinically contraindicated.

For all tumor biospecimen, tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) is not adequate and should not be submitted. The de novo biopsy(ies) should be formalin fixed and paraffin embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. Additional information on tumor biospecimen collection procedures is included in the Study Manual.

6.2. Treatment Period

For the purpose of scheduling evaluations, treatment cycles of 3 weeks during chemotherapy phase, and 6 weeks during maintenance phase, will be designated. To allow for patient and investigator schedules, holidays, and weather or other emergencies requiring clinical facilities to be closed, all patient visits can be performed ±3 days of scheduled visits on all cycles, as feasible. For details of on-treatment procedures see SOA table.

Patients will continue with the chemotherapy phase treatment, with or without avelumab, until progression of disease, a determination that the patient is no longer receiving clinical benefit, unacceptable toxicity, consent withdrawal, or death whichever comes first. Upon completion of chemotherapy, patients without evidence of disease progression (SD, PR or CR) will proceed to the maintenance phase of the study. Disease progression must be confirmed by BICR prior to withdrawal.

Patients receiving avelumab (Arms B or C) in the maintenance phase will continue treatment until progression of disease and determination that the patient is no longer receiving clinical benefit, unacceptable toxicity, consent withdrawal, a maximum duration of 24 months (not including chemotherapy phase), or death, whichever comes first.

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

In patients receiving avelumab up to the time of End of Treatment/Withdrawal visit, additional safety follow up must occur monthly for 90 days after the last dose of avelumab (Day 30 ± 3, Day 60 ± 3, Day 90 ± 3). The safety follow-up does not need to be performed for a patient who remains in maintainence and is undergoing safety assessments every 6 weeks.

Patients continuing to experience treatment related toxicity following discontinuation of study treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

Patients who discontinue study treatment for reasons other than disease progression will be followed until documented disease progression by BICR assessment regardless of the start of a new anti-cancer therapy. Tumor assessments should continue as specified in the SOA table until disease progression is documented by BICR assessment regardless of the start of new anti-cancer therapies.

Patients who discontinue study treatment (or, if on Arm A maintenance, reach End of Treatment/Withdrawal) will be followed every 12 weeks for survival status until death or until study completion, whichever is earlier will be followed every 12 weeks by telephone call for survival and subsequent therapies until death or the end of the study. The information collected for subsequent therapies should include details of the anti-cancer therapies, surgery, and date of initiation and discontinuation of each anti-cancer drug, and will be recorded in the CRF.

For End of Treatment/Withdrawal and Follow-Up visits procedures, see SOA.

6.4. End of Study

The study may end when at least 376 OS events have occurred within each of the two main comparisons (see Section 9.3 for further details).

For patients who remain on treatment with avelumab at the end of study, another source of access to avelumab will be proposed.

6.5. Patient Withdrawal

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

Reasons for study treatment/observation discontinuation may include, but are not limited to:

- Objective disease progression assessed by BICR. However, patients in the maintenance phase with disease progression who are continuing to derive clinical benefit may be eligible to continue with single-agent avelumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.3.1.3.1);
- Global deterioration of health status;
- Unacceptable toxicity (for patients on chemotherapy and/or avelumab). Patients who discontinue chemotherapy due to unacceptable toxicity in the absence of disease progression will enter maintenance phase and will continue to receive BSC (Arm A) or avelumab (Arms B and C). Patients who discontinue avelumab due to unacceptable toxicity during the chemotherapy phase may complete chemotherapy and then enter the maintenance phase with BSC.
- Pregnancy;

- Significant protocol deviation;
- Refusal of further treatment/patient request (patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures);
- Lost to follow-up (All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter.);
- Study termination by the Sponsor;
- Death.

Reasons for withdrawal from study follow-up may include, but not limited to:

- Completed study follow-up;
- Study terminated by Sponsor;
- Lost to follow-up;
- Refusal of further follow-up;
- Death.

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

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

7. ASSESSMENTS

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

7.1. Safety Assessments

Safety assessments will include collection of AEs, Serious Adverse Events (SAEs), vital signs, and physical examination, ECG (12-lead), and laboratory assessments.

7.1.1. Pregnancy Testing

For patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study treatment - once at the start of screening and once at the baseline visit, immediately before investigational product administration. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and another negative pregnancy result will then be required at the baseline visit before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period (both chemotherapy and maintenance phases), at the end of study treatment, during the post-treatment safety follow-up visits up to at least 60 days after the last avelumab infusion for patients receiving avelumab at the EOT/Withdrawal visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive hCG test, the patient will be withdrawn from administration of investigational product but may remain in the study.

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

7.1.2. Adverse Events of Special Interest for Avelumab

Patients will be monitored closely for toxicity. Any AE that is suspected to be a potential irAE is considered an AE of special interest (AESI). Specific guidance for the management of irAEs is provided in Section Table 7 Avelumab Management of Immune-Related Adverse Events. AESIs are reported according to the general AE reporting rules specified in Section 8.2.

7.1.3. Laboratory Safety Assessments

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the SOA and analyzed at local laboratories. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 11.

Table 11. Required Laboratory Tests

Hematology	Hemaglobin Platelets WBC Absolute Neutrophils Absolute Monocytes Absolute Eosinophils Absolute Basophils

Table 11. Required Laboratory Tests	
Chemistry Panel **(*denotes core chemistry panel)**	AST*° ALT*° Alkaline Phosphatase*° Sodium Potassium* Magnesium* Chloride* Total Calcium* Total Bilirubin*° BUN or Urea* Creatinine* Glucose (non fasted)* Phosphorus or Phosphate* Albumin*° Total Protein* Uric Acid Amylase Gamma glutamyl transferase (GGT)° Cholesterol Creatinine kinase° C reactive protein (CRP) Lactate dehydrogenase (LDH) Lipase Triglycerides
Urinalysis	Protein, glucose, blood
Coagulation Tests	PT or INR° aPTT
Pregnancy Tests	For female patients of childbearing potential, serum or urine
Thyroid Function Tests	TSH, free T4
Other Tests	ACTH, HBV, HCV serology, and CA-125

° For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.
ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, TSH=thyroid-stimulating hormone, WBC=white blood cell

7.1.4. Vital Signs and Physical Examinations

Patients will have physical examinations to include major body systems (a pelvic exam can be performed at the discretion of the Investigator), weight, blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the SOA table. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

7.1.5. Electrocardigram Assessments

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

All patients require a single ECG measurement at screening and on Day 1 of every other cycle during chemotherapy after carbo/taxol infusion on Arms A and B and after Avelumab infusion on Arm C. Additional ECGs will be performed on Day 1 of first maintenance cycle. Thereafter, on-treatment ECGs will be performed as clinically indicated.

Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc >500 msec, a subsequent should ECG should be repeated to verify the result. If ECG is confirmed >500 msec, local guidelines (eg, Repeat ECGs, review by cardiologist) should be followed.

7.2. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen, and pelvis CT or magnetic resonance imaging (MRI) scans. Brain CT or MRI scan at baseline is only required when there is suspected brain metastases or new lesion during the study. The CT scans should be performed with contrast agents unless contraindicated for medical reasons.

The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Tumor assessment will be performed at screening, after 3 cycles of chemotherapy, and at the completion of chemotherapy to determine eligibility for maintenance. For patients who undergo interval debulking surgery, an additional tumor assessment should be performed after surgery. During maintenance, anti-tumor efficacy will be assessed every 12 weeks until disease progression by BICR assessment. In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or rising CA-125 levels), and at the time of End of Treatment/Withdrawal (if not done in the previous 6 weeks). Complete and partial responses must be confirmed on repeat imaging ≥4 weeks after initial documentation. If radiologic imaging shows progressive disease (PD), then tumor assessment should be repeated after at least 4 weeks to confirm PD unless there is evidence of rapid clinical deterioration. See Section 5.3.1.3.1 regarding confirmation of progressive disease for patients receiving avelumab. Patients who come off study treatment without evidence of disease progression should be followed until progressive disease by BICR assessment with continued tumor assessments.

Bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of complete response for patients who have bone metastases.

Assessment of response will be made using RECIST version 1.1 (Appendix 3) CCI [redacted]
CCI [redacted]

[redacted]

All patients' files and radiologic images will be collected for Blinded Independent Central review (BICR), whose assessments will be used for the primary endpoint analysis (see Section 9.3).

7.3. Pathological Complete Response Assessment

Minimal requirements for interval debulking surgery and guidelines for assessment of pathologic complete response are described in Appendix 5.

7.4. Pharmacokinetic Assessments

Plasma/serum samples will be obtained from patients for PK analysis of avelumab, carboplatin, and paclitaxel as follows:

> **Arm A**: Serial PK for paclitaxel and carboplatin in the chemotherapy phase in at least 10 patients at selected sites.
>
> **Arm B**: Serial PK for paclitaxel and carboplatin in the chemotherapy phase in at least 10 patients at selected sites. Sparse sampling for avelumab in all patients in the maintenance phase.
>
> **Arm C**: Sparse sampling for avelumab in all patients in both the chemotherapy phase and maintenance phase. Serial PK for paclitaxel and carboplatin in the chemotherapy phase in at least 10 patients at selected sites.

Refer to the Schedule Of Activities for timing of the PK collections. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.4.1. Blood Sample Collection for Pharmacokinetic Analysis

Where noted in the SOA table, blood samples will be collected at approximately the same time as other assessments wherever possible. Blood samples should be drawn from the contralateral arm of the IV infusion.

PK samples will be collected from patients in all 3 treatment arms, Arms A, B, and C as described in the SOA table.

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

PK samples will be assayed for avelumab, carboplatin (total and free), and paclitaxel using validated analytical methods. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the study manual. As part of the

understanding of the PK of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for avelumab. The results of such analyses may be included in the clinical report.

7.4.2. Collection of Avelumab Pharmacokinetic Samples

A total of 3.5 mL of whole blood will be collected into a serum separator tube (SST) at the designated times to provide serum for avelumab PK analysis.

7.4.3. Collection of Carboplatin Pharmacokinetic Samples

A total of 5.0 mL whole blood sample will be collected into a plasma separator tube at the designated times in the SOA to provide plasma for carboplatin PK analysis.

7.4.4. Collection of Paclitaxel Pharmacokinetic Samples

A total of 3.5 mL whole blood sample will be collected into a plasma separator tube at the designated times in the SOA to provide plasma for paclitaxel PK analysis.

7.5. Immunogenicity Assessments

A total of 3.5 mL of whole blood will be collected into an SST at the designated times to provide serum for evaluation of avelumab immunogenicity. Immunogenicity blood samples will be assayed for anti-avelumab antibodies using a validated analytical method. All of the samples that are positive for ADA may also undergo characterization for neutralizing antibodies. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Study Manual.

7.6. Translational and Pharmacodynamic Assessments

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may identify those patients who benefit from treatment with the combination of avelumab and carboplatin/paclitaxel. In addition, analyses of sequentially obtained blood biomarkers will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment/Withdrawal visit will also help understand potential acquired mechanisms of resistance to the drug combination.

7.6.1. Tumor Biospecimens

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

Markers that may be analyzed include, but may not necessarily be limited to, PD-L1 expression and tumor infiltrating CD8+ T lymphocytes by IHC, and/or tissue expression of FoxP3, PD-1, PD-L2, homologous recombination deficiency testing on tumor tissue.

Samples from interval debulking surgery and optional tumor biopsies obtained upon disease progression (End of Treatment/Withdrawal) will be assessed in parallel with the mandatory pre-treatment biospecimens to provide data on changes in the tumor that accumulated over the course of therapy, including acquired mechanisms of resistance. For disease progression samples, only core needle or excisional biopsies, or resection specimens are suitable. Cytologic preparations, such as fine needle aspirate biopsies, are not acceptable. Additional information on tissue collection procedures can be found in the Study Manual.

7.6.2. BRCA 1/2 Mutation Status

BRCA 1/2 test result will be collected if it becomes known during the study.

7.7. Banked Biospecimens

7.7.1. Markers of Drug Response

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

To protect patients' confidentiality, the banked biospecimens and data generated from them will be coded with the patient's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the patient's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Patients can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Patients are notified in the informed consent document/patient information sheet that their results will not be given to them, unless

required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the patient's medical record. There is no intention to contact patients after completion of the clinical study.

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

7.7.2. Banked Biospecimens for Soluble Biomarker Assessments

Additional biospecimens to be retained for exploratory analyses in this study include the following:

- **Prep D1** (K2 edetic acid [ethylenediaminetetraacetic acid][EDTA] whole blood collection optimized for DNA analysis): A 4-ml blood biospecimen will be collected before start of the first infusion on Day 1 of every odd chemotherapy study cycle (all treatment arms). Additional samples will be collected on Day 1 of the second and fourth chemotherapy study cycles (all treatment arms). During the maintenance phase, samples will be collected on Day 1 of the first and second maintenance cycles only; and on Day 15 and 29 of the first and second maintenance cycles for patients randomized to Arms B and C. Samples to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, genes thought to be related to the mechanism of drug action, gene rearrangements, and epigenetic changes may be examined.

- **Prep B1.5** (EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis): A 4 mL blood specimen will be collected before start of the first infusion on Day 1 of every odd chemotherapy study cycle (all treatment arms). Additional samples will be collected on Day 1 of the second and fourth chemotherapy study cycles (all treatment arms). During the maintenance phase, samples will be collected on Day 1 of the first and second maintenance cycles only; and on Day 15 and 29 of the first and second maintenance cycles for patients randomized to Arms B and C.

- **Prep B2 (serum collection optimized for biomarker/ proteomics/metabonomic analysis):** A 10-mL blood biospecimen will be collected before the start of the first infusion on Day 1 of every odd chemotherapy study cycle (all treatment arms). Additional samples will be collected on Day 1 of the second and fourth chemotherapy study cycles (all treatment arms). During the maintenance phase, samples will be

collected on Day 1 of the first and second maintenance cycles only; and on Days 15 and 29 of the first and second maintenance cycles for patients randomized to Arms B or C.

- **Prep R1 (PAXGene whole blood collection optimized for RNA analysis)**: A 2.5-mL blood biospecimen will be collected before start of the first infusion on Day 1 of every odd chemotherapy study cycle (all arms). Additional samples will be collected on Day 1 of the second and fourth chemotherapy study cycles (all treatment arms). During the maintenance phase, samples will collected on Days 1 of the first and second maintenance cycles only; and on Days 15 and 29 of the first and second maintenance cycles for patients randomized to Arms B and C.

NOTE: For any of the biospecimens above, if a sample was collected at Screening, then it does not have to be collected at Day 1 of the start of chemotherapy prior to the infusion.

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

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

7.7.3. Additional Research

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

- Investigations of the disease under study in the clinical study, and related conditions;

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

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

7.8. Patient-Reported Outcomes Assessments

In the treatment of ovarian cancer it is important to increase survival and palliate symptoms while maintaining health related quality of life and minimizing treatment side effects.[50,51,52] To assess quality of life in clinical trials, patient reported outcomes (PROs) are frequently measured to quantify changes in disease specific symptoms, health related concerns, and

patient well- being. It is critical to assess the PROs using validated instruments.[53] In this trial, PROs will be assessed using 2 published and validated instruments: FOSI-18 and EUROQol5 dimension (EQ-5D-5L).

All patients will complete these two self-administered questionnaires pre-dose on Day 1 of every cycle during the chemotherapy phase, on Day 1 of every maintenance cycle (every 6 weeks), the End of Treatment visit, and every 6 weeks during the post treatment safety and survival follow-up period up to a total of 3 years from the date of patient enrollment. Patients must complete these questionnaires at the clinic prior to any study or medical procedure during the chemotherapy and maintenance cycles, and at home during the safety and survival follow-up period.

7.8.1. FOSI-18

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 Administartion (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.[54] 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.[55]

The FOSI-18 questionnaire will be administered as noted above and as per the SOA table. The amount of time for a patient to complete the questionnaire is estimated to be about 3 minutes.

7.8.2. EuroQoL EQ-5D-5L

The EuroQol EQ-5D-5Lis a 6-item patient completed questionnaire designed to assess health status in terms of a single index value or utility score.[56] There are 2 components to the EuroQol EQ-5D-5L: a Health State Profile which has individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self- care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.[57] Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction.

The EuroQol EQ-5D-5Lquestionnaire will be administered as noted on the SOA table. The amount of time for a patient to complete the questionnaire is estimated to be about 2 minutes.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product will be reported as described in the following sections.

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

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

8.2. Reporting Period

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

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the patient has taken at least 1 dose of investigational product through 90 calendar days after the last administration.

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

8.3. Definition of an Adverse Event

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

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

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

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

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

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

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

As for paclitaxel and carboplatin, an overdose is defined as a dose greater than the planned dose.

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

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

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

- Results in death;

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

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

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

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

  Concurrent with

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

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

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

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study treatment caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see Section 8.2 and 8.14 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

8.10. Exposure During Pregnancy

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

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

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (Also See Section 6.5 Patient Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

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

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

8.14.2. Non-Serious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The study is designed to test, in parallel, two hypotheses:

- The first null hypothesis is that the true PFS hazard rate for both platinum-based chemotherapy alone followed by observation (Arm A), and avelumab in combination with platinum-based chemotherapy followed by avelumab maintenance (Arm C), are the same (HR=1); versus the alternative hypothesis that the true hazard rate is smaller for Arm C than for Arm A (HR<1).
- The second null hypothesis is that the true PFS hazard rate for both, platinum-based chemotherapy alone followed by observation (Arm A), and platinum-based chemotherapy alone followed by avelumab maintenance (Arm B), are the same (HR =1); versus the alternative hypothesis that the true hazard rate is smaller for Arm B than for Arm A (HR<1).

Approximately 951 patients will be enrolled 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) vs adjuvant (incomplete resection >1 cm) vs neoadjuvant. Two hundred and seventy-two (272) PFS events within each comparison will be required to have 90% power to detect a hazard ratio of 0.65 using a one-sided log-rank test at a significance level of 0.0125.

The sample size for this study is determined based on the assumptions that the median PFS for patients treated with platinum-based chemotherapy alone followed by observation is 23 months,[6] 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 hazard ratio (HR) of 0.65 under the exponential model assumption. The sample size further assumes a 15% drop-out rate within each treatment arm, 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 cutoff for the primary PFS analyses 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.

If the true HR is 0.65 under the alternative hypothesis, 272 PFS events within each comparison will be required to have 90% power to detect a HR of 0.65 using a one-sided log-rank test at a significance level of 0.0125 (total significance level one-sided 0.025), 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 of 951 patients will also allow the assessment of difference in OS in the primary population. A total of 376 OS events, within each comparison, would be required to have 70% power to detect a HR of 0.75 (80% power to detect a HR of 0.725) using a one-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 for patients treated with platinum-based chemotherapy alone followed by observation is 80 months,[6] and the median OS for patients treated with avelumab in combination with

platinum-based chemotherapy followed by avelumab maintenance, or patients treated 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 cutoff for the final OS analysis will occur after the target number of events has been reached in both comparisons.

The study will be considered positive if at least one of the primary objectives is met.

9.2. Analysis Population

9.2.1. Full Analysis Set

The full analysis set will include all patients who are randomized. Patients will be classified according to the treatment and stratum assigned at randomization. The full analysis set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Per-Protocol Analysis Set

The per-protocol analysis set is a subset of the full analysis set and includes patients who received at least 1 dose of study treatment and do not have major protocol deviations expected to impact the primary objective of the study. Major protocol deviations will be pre-specified in the statistical analysis plan. The per-protocol analysis set will be used for sensitivity analyses for the primary efficacy endpoint.

9.2.3. Safety Analysis Set

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

9.2.4. Pharmacokinetics Analysis Set

The PK concentration analysis set is defined as all treated patients who have at least 1 concentration above the below limit of quantitation (BLQ) of avelumab.

The PK parameter analysis set is defined as all treated patients who have at least 1 of the PK parameters of interest of any of the 3 study drugs.

9.2.5. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all treated patients who have at least 1 ADA sample collected.

9.2.6. Biomarker Analysis Set

The biomarker analysis set is defined as all treated patients who have at least 1 screening biomarker assessment, and have received at least 1 dose of any study drug. Analysis sets will be defined separately for blood based and tumor tissue-based biomarkers.

9.3. Efficacy Analysis

All efficacy analyses will be performed on the full analysis set unless otherwise specified.

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

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

The primary analyses will be repeated on the per-protocol analysis set as a sensitivity analyses. All planned sensitivity analyses will be described in the SAP.

9.3.1. Analysis of the Primary Endpoint

The primary endpoint is PFS which is defined as the time from randomization to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurs first.

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

The primary analyses of PFS will be performed on the full analysis set, based on BICR assessment. A stratified log rank test (one-sided) stratified by randomization stratification factors will be used within each comparison at the interim and/or final analyses with the overall significance level preserved at 0.0125 (one-sided). PFS times associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25^{th}, 50^{th}, and 75^{th} percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

In addition, the PFS hazard ratio for Arm C vs Arm B will be calculated together with the 95% confidence interval.

PFS by BICR assessment will also be evaluated based on the per-protocol analysis set as a sensitivity analyses, using the stratified log-rank test (one-sided, α=0.0125).

9.3.2. Analysis of Secondary Endpoints

All analyses will be performed using the Full Analysis Set. The analysis of PFS using the Full Analysis Set described in Section 9.3.1 based on BICR assessment will be repeated based on the Investigator's assessment.

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

9.3.2.1. Overall Survival

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. Patients last known to be alive will be censored at date of last contact. OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary endpoint, PFS, is statistically significant at the PFS interim or final analyses. In addition OS will be tested at 50%, 75%, of the OS events and at the OS final analysis. Within each comparison, the analyses of OS will be performed based on the full analysis set. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses with the overall significance level preserved at 0.0125 (one-sided). OS time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratios and the corresponding 95% CIs.

In addition, the OS hazard ratio for Arm C vs Arm B will be calculated together with the 95% confidence interval.

9.3.2.2. Objective Response

Objective response is defined as a complete response (CR) or partial response (PR) per RECIST version 1.1 (Appendix 3) recorded from randomization until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as a non-responder in the OR rate (ORR) analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow up assessments) will be considered as non-responders in the ORR analysis.

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

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

9.3.2.3. Duration of Response

Duration of response (DR) is defined, for patients with an objective response per RECIST v1.1 (Appendix 3), as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS.

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

9.3.2.4. Maintenance Progression-Free Survival

Maintenance PFS is defined, for patients who proceed to maintenance 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 objective progression of disease (PD) or death due to any cause, whichever occurs first.

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 two or more missing tumor assessments. Patients who do not have a baseline tumor assessment or who do not have any on-maintenance tumor assessments 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 which case the death will be considered an event.

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

9.3.2.5. PFS2

PFS2 is defined as time from randomization to the start of second subsequent treatment after first progression, or death from any cause, whichever occurs first. If no date of second subsequent therapy is available, patients will be censored at date of last contact.

PFS2 will be summarized by treatment arm using Kaplan-Meier method and displayed graphically, where appropriate. The median PFS and 95% CI for the median will be provided for each treatment arm.

9.3.2.6. pCR

pCR is defined for neoadjuvant patients who undergo interval debulking surgery as the Chemotherapy Response Score 3 (CSR3) according to Bohm et al, 2015 and will be performed locally per guidelines provided in Appendix 5. An independent review of pCR may also be performed as necessary.

The pCR rate on each treatment arm will be estimated by dividing the number of patients who achieved pCR by the number of patients who were stratified as neoadjuvant. The corresponding exact 2 sided 95% CIs will be provided by treatment arm.

9.3.2.7. PFS by GCIG Criteria based on Investigator Assessment

PFS by GCIG criteria will be assessed in this study incorporating both RECIST 1.1 and CA-125 (see Appendix 6).[68]

PFS by GCIG criteria will be censored if both PFS by RECIST 1.1 and PFS by 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 treatment prior to an event, or for patients with an event after two or more missing CA-125 assessments. Patients who do not have a baseline CA-125 assessment or who do not have any post-baseline CA-125 assessments will be censored on the day of randomization, with a duration of 1 day.

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

9.3.2.8. Patient-Reported Outcomes

The FOSI-18 and EuroQol5 dimension (EQ-5D-5L) will be scored according to their respective validation papers and user's guides.[54,56,57]

As the primary PRO analysis, the FOSI-18 total score will be assessed to determine if overall HRQoL has been impacted over the course of the study among the 3 treatment arms for the comparisons Arm C vs Arm A and Arm B vs Arm A. Random coefficient modelling will be carried out for the FOSI-18 total score. Additionally, summary statistics [mean (and standard deviation), median, range and 95% CI] of absolute scores will also be reported for this total score. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of this score over time will be provided for each treatment arm. The primary analysis will be applied to all cycles, chemotherapy and maintenance phases, before progression. A secondary analysis will include all assessments, including post-progression data for those patients who progress during the three year PRO follow up period.

Several secondary PRO analyses will be conducted. A single question within the TSE subscale ("I am bothered by side effects of treatment") will be assessed among the 3 treatment arms for the comparisons Arm C vs Arm A and Arm B vs Arm A. The analysis will be applied to the post-chemotherapy period until EOT. Random coefficient modelling will be carried out for the single question score. Additionally, time to development of significant side effect bother (TTB) will be analyzed where a TTB event will be defined as the 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 last time when they completed a FOSI-18 assessment if they have not had a TTB event. Additionally, summary statistics [mean (and standard deviation), median, range and 95% CI] of absolute scores will also be

reported for this question. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of this question over time will be provided for each treatment arm.

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 first dose (baseline) 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 last time when they completed a sub-scale assessment if they have not deteriorated. Yost & Eton established that a 3-point or a greater group difference on a FACT scale of this length (9 items for FOSI DRS-P subscale) constitutes a meaningful difference between groups in disease symptoms.[58]

TTD of the FOSI DRS-P will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided and the unstratified log rank test will be the primary method to compare (pairwise) the time to first deterioration for Arm C vs. Arm A and Arm B vs. Arm A. The median TTD and 2 sided 95% CI for the median will also be provided based on the Brookmeyer Crowley method [Brookmeyer 1982].[59]

Patient reported disease-related symptoms-emotional (DRS-E), treatment side effects (TSE) using all of the questions including the single "treatmentbother' question, and function/well-being (FWB) will also be assessed across all three treatment arms. Summary statistics [mean (and standard deviation), median, range and 95% CI] of absolute scores will be reported for all of these subscales of the FOSI-18 questionnaire and the EQ-5D-5LVAS scale. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm. Additional exploratory analyses may be performed such as random coefficient models to assess the pairwise differences among the treatment arms.

For the EQ-5D-5Lhealth state profiles, the proportions of patients reported having "none", "slight", "moderate", "severe", or "extreme/unable" problems at each time point will be reported.

9.3.2.9. Pharmacokinetic Analysis

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.

9.3.2.9.1. Pharmacokinetic Analysis of Avelumab

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

9.3.2.9.2. Pharmacokinetic Analysis of Carboplatin and Paclitaxel

Standard plasma PK parameters for carboplatin and paclitaxel will be estimated using non-compartmental and/or compartment methods, if needed. Analysis and will include C_{max}, T_{max}, $AUC_{0\text{-}tau}$, $t_{½}$, plasma clearance (CL), and volume of distribution (Vd) as data permit. Dose-normalized parameters (eg, CDN-Cmax, DN-AUC) will be reported as appropriate). Descriptive statistics for the PK parameters for carboplatin (total and free) and paclitaxel will be provided by cycle and day of assessment in tabular form.

Carboplatin (total and free) and paclitaxel plasma concentrations will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% confidence interval) by cycle, day, and nominal time. Individual patient and median profiles of the profiles will be presented on both linear-linear and log-linear scales.

9.3.2.9.3. Effect of Avelumab on Carboplatin/Paclitaxel

The effect of avelumab dosing on carboplatin and paclitaxel PK will be evaluated based on overall assessment of the geometric mean ratios for C_{max}, AUC_{24}, AUC_{inf} of carboplatin and paclitaxel on Day 1 of the fourth chemotherapy cycle in Arm C (carboplatin/paclitaxel + avelumab) compared to those on Day 1 of the fourth chemotherapy cycle of Arm B.

9.3.2.9.4. Effect of Carboplatin/Paclitaxel on Avelumab Pharmacokinetics

The effect of carboplatin/paclitaxel dosing on avelumab PK will be evaluated based on the overall assessment of the geometric mean ratios of C_{max} and C_{trough} of Arm C on Day 1 of the second chemotherapy cycle compared to those on Day 1 of the first maintenance cycle of Arms C and B.

9.3.2.10. Immunogenicity Analysis

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

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

9.3.2.11. Exposure/Response Analysis

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

9.3.3. Biomarker Analysis for Secondary and Exploratory Endpoints

Biomarker status (ie, positive or negative) may be determined by a predictive biomarker test with an established scoring algorithm defining positive and negative that is developed by the Sponsor. Analysis of primary and secondary efficacy endpoints in subgroups defined by

biomarker status will be performed and reported as described above. Comparisons will be made between biomarker subgroups (positive and negative) within treatment arms and between treatment arms within biomarker subgroups.

9.4. Analysis of Exploratory Endpoints

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

9.5. Safety Analysis

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

9.5.1. Adverse Events

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

Emphasis in the analysis will be placed on AEs classified as treatment emergent. Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade ≥3, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for AEs of clinical interest may be further assessed as described in the SAP.

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

9.5.2. Laboratory Abnormalities

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

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

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

9.5.3. Electrocardiograms

ECG measurements will be used for the statistical analysis and all data presentations. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

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

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post baseline corrected QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment. Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

9.6. Interim Analysis

The interim analysis (IA) will be performed based on the full analysis set. Any safety evaluation at the time of the IA will be based on the safety analysis set.

The goals of the interim analysis are to allow early stopping of the treatment arm (Arm B or Arm C) or the study for futility or efficacy, to assess the safety of avelumab alone or in combination with platinum-based chemotherapy. The interim analysis for both comparisons will be performed at the same time.

The study is designed to have, within each hypothesis testing, one interim analysis and the final analysis based on the primary PFS endpoint. A formal efficacy boundary (O'Brien-Fleming) for rejecting the null hypothesis is constructed by using the spending function methodology of Lan-DeMets. To protect the integrity of the study and to preserve the type 1 error rate, a fraction of alpha (0.0022) for efficacy will be spent at the interim analysis and accounted for in the overall type 1 error rate if the interim analysis is performed exactly 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.[60] The overall significance level for the efficacy analysis of PFS, within each comparison, will be preserved at 0.0125 (1-sided test).

Within each comparison, the interim analysis will be performed after approximately 181 PFS events (2/3 of the 272 events planned for each comparison at the end of the study). If the value of the test statistic exceeds the efficacy boundary ($z < -2.848$, $p < 0.002$), then the experimental treatment (or the study) may be stopped for efficacy. If the value of the test statistic exceeds the futility boundary ($z > -0.804$, $p > 0.211$), then the experimental treatment (or the study) may be stopped for futility.[61] If the results of the interim analysis indicate serious safety concerns, the Sponsor will communicate with the Health Authorities regarding stopping the relevant experimental arms or the clinical trial.

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 its respective avelumab-containing arm (ie, Arm B or Arm C). Within each comparison, a maximum of 5 analyses are planned for OS: at the time of the interim PFS analysis, at the time of the final PFS analysis, at 50%, 75%, and 100% (final OS analysis) of the 376 OS events. An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis will be used to preserve the 0.0125 overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and final analyses. 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 favouring its respective avelumab-containing arm.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC) comprised of 2 independent clinicians and 1 independent statistician.

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Patient Information and Consent

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

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

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

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

The investigator must ensure that each study patient, or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

12.4. Patient Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

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

13.2. End of Trial in All Other Participating Countries

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

14. SPONSOR DISCONTINUATION CRITERIA

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

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for

Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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

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

[redacted]

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Appendix 1. Abbreviations

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

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	target area under the concentration
BICR	Blinded Independent Central Review
BLQ	Below limit of quantitation
BRCA	breast cancer antigen
BSC	best supportive care
BUN	Blood urea nitrogen
CI	confidence interval
CR	complete response
CRF	case report form
CRP	C-reactive protein
CSR3	Chemotherapy Response Score 3
CSA	clinical study agreement
CSF	cerebrospinal fluid
CT	computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	Dosing and Administration Instruction
DCIS	ductal carcinoma *in situ*
DCR	disease control rate
DL	dose level
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	duration of response
DRS-E	disease-related symptoms-emotional
DRS-P	disease-related symptoms-physical
DU	dispensable unit

Abbreviation	Term
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Group
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EOS	end of study
EPO	erythropoietin
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FIGO	International Federation of Gynecology and Obstetrics
FACIT	Functional Assessment of Chronic Illness Therapy
FSH	follicle-stimulating hormone
FTC	fallopian tube cancer
FWB	function/well-being
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferae
GI	gastrointestinal
GMP	Good Manufacaturing Practice
GOG	Gynecologic Oncology Group
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICU	intensive care unit
ID	identification
IFN	interferon

Abbreviation	Term
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IL-6	interleukin-6
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
irAE	immune-related adverse event
IRB	institutional review board
CCI [redacted]	[redacted]
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
JGOG	Japanese Gynecologic Oncology Group
LCIS	lobular carcinoma *in situ*
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LPLV	last patient last visit
MID	minimally important difference
MRI	magnetic resonance imaging
N/A	not applicable
Nab	neutralizing antibody
NCCN	National Cancer Comprehensive Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OC	ovarian cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PCD	primary completion date
pCR	pathological complete response
PD	progression of disease
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics

Abbreviation	Term
PLT	platelet
PPC	primary peritoneal cancer
PR	partial response
PROs	patient-reported outcomes
PT	prothrombin time
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SD	stable disease
SOA	Schedule of Activities
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SST	serum separator tube
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TO	target occupancy
TSE	treatment side effect
TSH	thyroid stimulating hormone
TTB	Time to side effect bother
TTD	time to deterioration
UICC	Union for International Cancer Control
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
VAS	visual analogue scale
WBC	white blood cell count

Appendix 2. ECOG Performance Status

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

Appendix 3. RECIST Version 1.1

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

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non measurable disease

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

- Bone disease: Bone disease is non measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non measurable unless it has progressed since completion of treatment.

Normal sites

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

RECORDING TUMOR ASSESSMENTS

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

Target lesions

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

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

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

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

Non target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

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

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

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

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

- Indeterminate. Progression has not been documented, and

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

    or

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

    or

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

    or

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

Non target disease

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

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

- PD: Unequivocal progression of pre existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

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

Supplemental Investigations

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

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

Objective/Subjective Progression

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

Table 12. Objective Response Status at each Evaluation

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

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

Table 13. Objective Response Status at each Evaluation for Patients with Non Target Disease Only

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

Determination of Best Overall Response

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

CCI

[redacted]

CCI

[redacted]

Appendix 5. Guidelines for Interval Debulking Surgery and Assessment of Pathological Complete Response

Pathological complete response has been shown to provide valuable prognostic information in patients with various tumor types, such as breast cancer or colorectal cancer, who received neoadjuvant therapy.

Compared to breast cancer, there is relatively little experience with using the rate of pCR as a surrogate endpoint in ovarian cancer. There are also challenges in standardization of pCR assessment, since unlike breast cancer it is difficult to accurately sample the entire tumor bed.

A recent study by Bohm et al, 2015, has tested and validated the prognostic significance of a 3-tier scoring system for grading pathological response to neoadjuvant therapy in patients with high-grade pelvic serous carcinoma. The study included 60 patients in the test cohort and 71 patients in the validation cohort.

This 3-tier scoring system is reproducible, simple and easy to apply, and shows a significant association with clinical outcome when based on pathological assessment of omentum samples.

This is the grading system currently recommended by the Ovary, Fallopian Tube and Primary Peritoneal Carcinoma ICCR (International Collaboration on Cancer Reporting) Histopathology Reporting Guide, version 0.5.[73,74]

In this protocol, the following guidelines for surgery and pathologic assessment, fully aligned with the ICCR reporting guide described above, were developed with the aim of standardizing the assessment of pCR.

Minimum requirements for interval debulking surgery:

- bilateral salpingoophorecotmy
- hysterectomy
- infracolic omentectomy
- palpation and visualization of all entire peritoneal surfaces with resection or biopsy of all suspicious areas

The details of the surgery will be collected in the CRF.

Minimum requirements for pathologic assessment of interval debulking surgery specimens:

Pathologic assessment should be performed as follows.

- **Macroscopic description of omentum**

  Three dimensions of the omentum should be provided in the pathology report to document the size of the specimen received for pathological examination. Examination of 4-6 blocks of omentum is recommended. The size of the largest tumour deposit should be recorded in the pathology report.

- **Response to neoadjuvant therapy**

  1. Scoring should be carried out on a single H&E-stained section.

  2. A single block of involved omental tissue that shows the least response to chemotherapy should be selected (if there is no residual omental tumour a Chemotherapy Response Score/CRS score of 3 is given - see table below)

  3. The amount of viable tumour should be assessed; this may or may not show degenerative changes in the form of nuclear atypia, smudging of the nuclear chromatin and cytoplasmic clearing.

  4. Tumor regression grading should be scored using a 3-tier system as outlined in Table 15 below:

Table 15. Criteria for Chemotherapy Response Score

Score	Definition
CRS1	No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration.
CRS2	Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable.
CRS3	Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases no or very little residual tumor in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is microscopic residual tumor present.

NOTE: Regression-associated fibroinflammatory changes consist of fibrosis associated with macrophages, including foam cells, mixed inflammatory cells, and psammoma bodies, as distinguished from tumor-related inflammation or desmoplasia.

  5. The presence of fibrosis may be helpful in marking the site of previous tumour infiltration.

- When found in the absence of tumour, fibrosis is likely to indicate regression.
- If fibrosis occurs in association with tumour, this may simply reflect tumour-associated desmoplasia rather than regression.
- However, when fibrosis in association with tumour is accompanied by an inflammatory response (so-called 'fibro-inflammatory' response - fibrosis with associated macrophages and a mixed population of inflammatory cells), this indicates regression.
- Psammoma bodies may mark the site of previous tumour and can sometimes appear more numerous because their density increases in areas where tumour has disappeared.

6. As a guide, >95% of tumour should be viable for a score of 1, and <5% for a score of 3.

Assessment of residual viable tumor:

In addition to the Chemotherapy Response Score 3-tier scoring system for grading pathological response, all surgical specimens, including the adnexa, will be assessed for the presence or absence of residual neoplastic cells (viable tumor present vs. absent).

Appendix 6. PFS by GCIG Criteria

As described in published guidelines,[68] progression by GCIG criteria will be defined as progression by RECIST 1.1 OR progression by CA-125.

Progression or recurrence based on serum CA-125 levels will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart, OR

2. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value on 2 occasions at least 1 week apart, OR

3. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA-125 progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA-125 if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have PD on the basis of either the objective RECIST 1.1 criteria or the CA-125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.