CLINICAL PROTOCOL

A RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE 3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AVELUMAB IN COMBINATION WITH CHEMOTHERAPY FOLLOWED BY MAINTENANCE THERAPY OF AVELUMAB IN COMBINATION WITH THE POLY (ADENOSINE DIPHOSPHATE [ADP]-RIBOSE) POLYMERASE (PARP) INHIBITOR TALAZOPARIB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED OVARIAN CANCER

JAVELIN OVARIAN PARP 100

Investigational Product Number:	MSB0010718C MDV3800, BMN 673
Investigational Product Name:	Avelumab Talazoparib
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	EudraCT 2017-004456-30
ClinicalTrials.gov Registry Number:	NCT03642132
Protocol Number:	B9991030
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 2	06 June 2019	The JAVELIN Ovarian 100 study (B9991010) was stopped due to futility of efficacy at a planned interim analysis, and therefore, the Sponsor decided to stop enrollment in the JAVELIN Ovarian PARP 100 study (B9991030). On 19 March 2019, a Dear Investigatior Letter was issued to notify the investigational sites that no new patients could be screened or randomized. Patients who remain in the study will continue receiving investigational products according to their randomized treatment assignment and will be monitored for appropriate safety assessments until treatment discontinuation. The purpose of protocol amendment 2 is to reduce study-specific procedure assessments (ie, efficacy, physical examination, electrocardiogram, ePROs and tumor assessments, PK and Biomarkers) for the ongoing patients. The original schedule of activities (SOA) has been replaced by a new SOA found in Appendix 6. The following sections were modified based on the above: • Protocol Summary Section: Added enrollment termination rationale to the Protocol Summary section. • 1.2.2.2. Safety of Avelumab Combined with Carboplatin and Paclitaxel in Ovarian Patients: Added that no new safety signals were identified from the B9991010 study relative to the known safety profile of avelumab or the other study medications. • 1.2.3.2. Clinical Efficacy of Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA 1/2 Mutation): Added the approval of talazoparib in United States and

		European Union. • 1.2.3.3 PARP Inhibitor in Ovarian Cancer: Added results from the Phase 3 SOLO-1 study that led to the approvals of olaparib. • 2. Study Objectives and Endpoints: The original study objectives and endpoints are no longer applicable and/or feasible. • 3.1.1 Study Treatment Plan: Removed wording related to BICR assessment per RECIST v1.1, new anti-cancer therapy and tumor assessments. No longer requiring BICR. Patient can receive study treatment until progressive disease as assessed by the investigator according to institutional local guidelines. • 3.2 Safety Monitoring and 9.10 Data Monitoring Committee: Use of an External Data Monitoring Committee is no longer applicable. • 5. Study Treatments and 5.5.1 Avelumab Plus Talazoparib: Removed wording related to BICR assessment. Disease progression is to be confirmed based on investigator assessment. • Table 9. Modification Guidance for Hematologic Toxicity: Updated row 1 DLT-PLT from Yes to No due to a typographical error. • 5.7 Treatment after Initial Evidence of Radiological Disease Progression: Removed wording related to BICR assessment. Disease progression is to be confirmed based on investigator assessment. • 5.10. Concomitant Treatment, Radiotherapy, and Surgery: Minor updates including concomitant medications and treatments will not be captured in the INFORM database unless they contribute or are associated with the treatment for an AE/SAE. • 5.10.2.1 Interval Debulking Surgery: May be

		performed according to local guidelines or standard of care at the discretion of the investigator. Removed wording related to BICR.
		
		• 5.10.2.2 Other Surgery: Removed wording related to second debulking surgery and subsequent anti-cancer therapy. No longer required to be reported on the eCRF.
		
		• 5.10.5 Corticosteriods & 5.10.6 Other Prohibited Concomitant Medicines and Therapies: Modified this section to allow for therapeutic and/or prophylactic corticosteroids to be used as needed per standard of care.
		
		• 6. Study Procedures: The following was updated:
		
		  • Screening: Obsolete.
		
		  • Treatment Period and End of Treatment: Removal of RECIST v1.1 and BICR wording as well as reference to PK specimens and genomic banked specimens as they are no longer being collected.
		
		  • Short-Term and Long-Term Follow-up: Removal of long-term and survival follow-up wording.
		
		• 7.1 Safety Assessments: Physical examination, ECOG and ECG are not required per protocol but may be performed as clinically necessary.
		
		• 7.1.4 Laboratory Assessments: Do not need to be recorded in the INFORM database, unless the findings support an AE/SAE. Also, updated and removed certain previously required safety laboratory tests that are no longer required.
		
		The following assessments will no longer be collected as outlined in Section 7:
		
		• Pharmacokinetic (Avelumab and Talazoparib);

		• Immunogenicity; • Biomarker and Pharmacodynamic; • Tumor Tissue Sample; • Banked Biospecimens; • Tumor Response Assessments including scans; • Patient Reported Outcomes. 9. Data Analysis/Statistical Methods section was updated to reflect the following: As of 19 March 2019, the Sponsor made the decision to stop enrollment/randomization in study B9991030. Patients who were randomized can continue treatment and will be monitored for appropriate safety assessments until treatment discontinuation. As of 19 March 2019, approximately 11% of the patients originally planned to be randomized in the study had been randomized. Therefore, the study endpoints are no longer applicable and/or feasible. No formal statistical analyses will be conducted, but patient characteristics, duration of treatment and safety data will be summarized by treatment arm. Only the Safety Analysis Set, Pharmacokinetic Analysis Set and Immunogenicity Analysis Set are applicable. All randomized patients received at least 1 dose of study drug in the study; therefore, the safety analysis set will also be used for patient characteristics. The results of the pharmacokinetic analyses on samples collected prior to IRB/EC approval of protocol amendment 2 will not be included in the Clinical Study Report but will be retained by the Sponsor and may be pooled with data from other studies to further inform the development programs of avelumab and talazoparib, as appropriate.

		The interim analysis is no longer applicable. Marked the following Appendices as Obsolete: • 3. Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Guidelines; • 4. PFS by GCIG Criteria; • 5. Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C). Added Appendix 6. Revised Schedule of Activities.
Protocol Amendment 1	11 October 2018	1. Reduction of Talazoparib starting dose to lower the risk for treatment emerging adverse events that require dose modifications and improve long-term tolerability in the maintenance setting. The following sections were modified: • 1.0 (Introduction); • 1.2 (Background and Rationale); • 3.1.1 (Study Treatment Plan); • 5.3.1.2 (Talazoparib); • 5.5 (Administration of Bevacizumab Plus Chemotherapy); • 5.6.1 (Dose Reductions for Talazoparib); • 5.6.2 (Study Treatment Modifications for Drug-related Toxicity from Avelumab and Talazolparib). 2. Modifications to align with USPI for bevacizumab. Changed maximum duration of bevacizumab treatment to 21 or 22 doses per local approval. The following sections were modified: • 3.1.1 (Study Treatment Plan); • 6.2 (Treatment Period).

		3. Modifications to align with updated Investigator Brochure for Talazoparib dated August 2018. Extended duration of contraception and concomitant medication interactions, and updated with most recent PK data. The following section were modified: • 1.2.3.3 (Pharmacokinetics of Talazoparib in Humans); • 4.1 (Inclusion Criteria); • 4.3 (Lifestyle Requirements); • 5.6.3 (Overdose of Talazoparib); • 5.10.6 (Other Prohibited Concomitant Medications and Therapies); • 5.10.7 (Cautionary Use of Concomitant Medicines While on Treatment with Talazoparib; • 7.1.2 (Contraception Check). 4. Modifications based on Health Authority request to collect temperature and ECG at the start and end of maintenance treatment and add Acute Myeloid Leukemia to Exclusion criteria #10. The following sections were modified: • Schedule of Activities (Table 1 & 2); • 4.2 (Exclusion Criteria); • 7.1.5 (Vitals Signs and Physical Examination); • 7.1.6 (Electrocardiogram Assessments). 5. Clarified DDR+ definition to align with Foundation Medicine's approved CDx. The following section was modified: • 1.2.7 (Rationale for Biomarker Assessments).

		CCI [redacted] CCI [redacted] 7. To be consistent and align with avelumab program the tumor assessment time point at End of Treatment/Withdrawal was updated to indicate tumor scans do not need to be repeated if performed within 6 weeks of EOT/Withdrawal visit. • Table 1. & 2. SOA footnote #40: End of Treatment/Withdrawal was updated to remove 12 weeks and replaced with 6 weeks. 8. There are no scheduled visits requiring assessments on Days 8, 15, 29 and 36 in Arm C. Removed Days 8, 15, 29 and 36 from the Table 2.0 SOA (Arm C). 9. Added ClinicalTrials.gov Registry Number to title page. 10. Removed statement that tumor tissue must contain 40% or greater tumor nuclei per central laboratory assessment from inclusion criterion #4 to avoid non-compliance with source verification at time of screening. This requirement is provided in protocol Section 7.4.1 Baseline Tumor Tissue and in the central laboratory manual.

		11. Modifications were made for administrative changes, typographical corrections, and for clarity and consistency including but not limited to the following sections: • Table 1. SOA Footnote 6 corrected from Day 22 to Day 29 of each maintenance cycle for hematology and blood chemistry (PACL 12Jun2018); • Table 1. SOA Footnote 10 updated to specify serum/urine pregnancy test and clarify time point descriptions in SOA table to align with Section 7.1.1. Pregnancy Testing (PACL 12Jun2018 and 11Jul2018); • Table 1. SOA Footnote 28: corrected blood volume from 3.5 to 3.0 mL for PK blood sample (PACL 12Jun2018); • Table 2. SOA added ECOG Performance Status collection at Day 1 of each chemotherapy cycle to align with protocol Section 7.1.5 Vital Signs and Physical Exam (PACL12Jun2018); • Table 2. SOA updated to reflect that pregnancy testing is not required during short-term follow-up (Day 30, 60, and 90), [PACL11Jul2018]); • Table 2. SOA footnotes 37 and 38 corrected to align with SOA table (PACL 11Jul2018); • Section 1.2.5.1 (Rationale for Investigational Product Doses - Avelumab) removed reference to Arm B given that avelumab is only administered in Arm A (PACL 11Jul2018); • Section 5.2 (Patient Compliance) clarified to state that time of dose for talazoparib is not collected (PACL 11Jul2018); • Table 7. Management of Immune-Related Adverse Events updated to align with

		current IB v.8 for avelumab; • 10.4 Pharmacokinetic Analysis was updated to remove operational instructions for study team members about PK blinding; • 10.4.1 PK Analysis for Avelumab and Talazoparib was updated to remove text that is not applicable to this study.
Original Protocol	30 March 2018	Not applicable (N/A)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. 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.[27] Although expectations for long-term survival can be high if the cancer is identified and treated early, the 5-year survival rate for women diagnosed with advanced ovarian cancer is less than 30% from statistics in the United States and less than 20% in the United Kingdom.[28,29]

Ovarian neoplasms consist of several histopathological entities. Epithelial ovarian cancer (EOC) comprises the majority of malignant ovarian neoplasms (about 80%);[30] however, other less common pathologic subtypes must be considered in treatment recommendations, eg, fallopian tube cancer (FTC) and primary peritoneal cancer (PPC) which are less common neoplasms, are managed in a similar manner to EOC.

Carboplatin in combination with paclitaxel is the current standard of care in the front-line EOC treatment setting. Complete response is achieved in approximately 75% of patients, but the median progression-free survival (PFS) is approximately 18 months and most patients ultimately succumb to the disease.[30] 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.

Several studies have been conducted in the frontline treatment setting. Due to long post-progression survival and the potential for post-treatment crossover to confound overall survival (OS) results interpretation, PFS is an accepted endpoint in this setting.[31] Bevacizumab (Avastin®, Genentech, Inc.) in combination with chemotherapy followed by maintenance therapy (16 cycles or 48 weeks in Gynecologic Oncology Group (GOG)-218 study, 12 cycles or 36 weeks in International Collaboration on Ovarian Neoplasms (ICON) 7 study) demonstrated improvement in PFS in the front-line treatment setting[32,33] but without statistically significant improvement on OS.[35] Both trials focused on patients who were at high-risk for recurrence; ICON 7 allowed Stage I and II patients considered high risk for recurrence (high-grade), whereas GOG-218 included only patients with Stage III and IV disease. In ICON 7, 31% of patients had Federation of Gynecology and Obstetrics (FIGO) Stage III or IV disease and >1 cm residual disease after debulking surgery and in GOG-218, 66% of patients had Stage III and >1 cm residual disease or Stage IV. Bevacizumab is currently approved in the frontline, platinum-sensitive recurrent setting, and platinum-resistant recurrent treatment settings in the European Union (EU)[57] while in the United States (US), it is approved in the platinum-sensitive recurrent and platinum-resistant treatment setting. Despite this lack of approval in the US, bevacizumab is routinely used both in the US and EU in the frontline setting. Subsequent to the original protocol, on June 13, 2018, the Food and Drug Administration (FDA) approved bevacizumab for use in the frontline setting.[58]

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.[36] A randomized study demonstrated non-inferiority of this approach with respect to overall survival compared to adjuvant therapy in high-risk patients.[21] 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.[31] A number of frontline studies have successfully enrolled patients undergoing either adjuvant or neoadjuvant therapies in the same trial (GOG-262 and ICON 8). ICON 8 results comparing neoadjuvant and adjuvant treatment are pending. The primary analysis of GOG-262 was published in 2016.[32] In GOG-262, the primary research question was whether dose dense paclitaxel could improve outcome in incompletely resected Stage III or IV disease. Both neoadjuvant and adjuvant were (pre-specified) treatment options, as well as the addition of bevacizumab. The primary endpoint was not met. Dose dense paclitaxel was not superior to the every 3 weeks (Q3W; standard) paclitaxel regimen. A pre-specified subgroup analysis showed that in the absence of bevacizumab, there was a benefit for dose dense paclitaxel (median PFS [mPFS] 14.2 months versus 10.3 months, hazard ratio 0.62, 95% confidence interval [CI]: 0.40, 0.95, p=0.03). In the presence of bevacizumab, there was no difference in mPFS (14.9 versus 14.7 months).

The current standard of care in the frontline maintenance treatment setting is region-dependent. A significant number of patients, especially those with poor prognostic factors (incompletely resected Stage III and Stage IV), receive bevacizumab in combination with induction chemotherapy followed by bevacizumab maintenance therapy in regions where bevacizumab is available in this setting. For others, especially those with fewer poor prognostic factors, a standard of care option includes platinum doublet chemotherapy followed by best supportive care/observation or participation in a clinical trial.

Avelumab and talazoparib have the potential to produce additive or synergistic anti-tumor activity, with talazoparib functioning to promote immune priming and tumor immunogenicity and avelumab functioning to overcome Programmed Death Ligand 1 (PD-L1) mediated inhibition of any resulting anti-tumor immune response.

Specifically, the activity of avelumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells.[21] Talazoparib, via its ability to promote increased DNA (deoxyribonucleic acid) damage, has the potential to promote several of these key stages of the immune response.

Ovarian cancer has been reported to a have high prevalence (~20%) of defects in the BRCA (BReast CAncer Gene) 1/2 genes, which have been reported to predict for sensitivity to PARP inhibitors,[43] such as talazoparib. Ovarian tumors harboring such defects have also been shown to present with increased PD-L1 expression and increased T-cell infiltration.[44,46] Increased T-cell infiltration has been associated with improved outcome in ovarian cancer,[45] and both increased T-cell infiltration and PD-L1 expression have been associated with improved response to anti-PD-1)/PD-L1 treatment.[46] Given these data, tumors harboring

these defects may respond more robustly to combination treatment with talazoparib and avelumab.

Ovarian cancer has been reported to have a high prevalence (≥35%) of genomic scarring. Tumors with a high level of genomic scarring have been shown to have increased clinical benefit from PARP inhibitors,[48,49] and as such might also be expected to respond more robustly to the combination of talazoparib and avelumab.

Given the intrinsic links between DNA damage and immune priming outlined above, and the potential for PARP inhibition to promote DNA damage in the presence of DNA damage repair (DDR) defects, ovarian cancer, with its high prevalence of such defects, represents a tumor type in which the combination of talazoparib and avelumab may optimally mediate anti-tumor activity.

Considering the above described mechanism of action and the preliminary clinical activity observed for the investigational products or agents of the same class (see Section 1.1.1 and Section 1.1.2), the avelumab and talazoparib combination is proposed for evaluation in patients with advanced epithelial ovarian cancer.

On 21 December 2018, the Sponsor (Pfizer and Merck KGaA) announced that the Phase 3 JAVELIN Ovarian 100 study (B9991010) was stopped due to futility of efficacy at a planned interim analysis in alignment with the recommendation of both the Independent Data Monitoring Committee and the Protocol Steering Committee. There were no new safety signals identified from the B9991010 study relative to the known safety profile of avelumab or the other study medications.

Detailed analyses of the data from study B9991010 have since been performed to determine the impact on the ongoing JAVELIN Ovarian PARP 100 study (B9991030). Although the overall safety profile of avelumab remains unchanged, the lack of efficacy with avelumab in the treatment of frontline ovarian cancer observed in study B9991010 reduces the probability of technical success of study B9991030 and of regulatory success of any submission based on this study.

In addition, the recent approvals in the United States and in the European Union of a PARPinhibitor in the front-line maintenance setting based on the practice-changing results from the SOLO-1 trial (National Clinical Trial # 01844986) provide a sound rationale for PARP inhibitor therapy instead of bevacizumab for patients with deleterious germline or somatic BRCA mutations. This new treatment paradigm creates a recruitment challenge for enrolling BRCA+ patients into the B9991030 study along with a risk for high attrition of BRCA+ patients when randomized to the bevacizumab control arm.

Therefore, based on the totality of the information, the Sponsor made the decision to stop enrollment in the B9991030 study. On 19 March 2019, a Dear Investigatior Letter was issued to notify the investigational sites that no new patients could be screened or randomized.

Patients who had been randomized prior to 19 March 2019 were able to remain in the study provided they sign the Informed Consent Addendum upon its approval by local institutional review board (IRB)/ethics committee (EC). Patients who remain in the study will continue receiving investigational products according to their randomized treatment assignment and will be monitored for appropriate safety assessments until treatment discontinuation.

Objectives and Endpoints (Obsolete)

The original study objectives and endpoints are no longer applicable and/or feasible.

The purpose of protocol amendment 2 is to reduce study-specific procedure assessments (ie, remove efficacy, physical examination, electrocardiogram, ePROs, tumor assessments, pharmacokinetics (PK) and Biomarkers) for the ongoing patients.

The schedule of activities (SOA) found in Appendix 6 is replacing the previous SOA and has been revised to decrease the frequency of study procedures while maintaining appropriate assessment of patient safety. The new SOA is effective with IRB/EC approval of amendment 2.

Primary Objective(s):	**Primary Endpoint(s):**
• To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging PFS in patients with advanced ovarian cancer with defects in DNA damage repair (DDR+).	• PFS as determined based on BICR assessment per RECIST v1.1 in patients with newly diagnosed advanced ovarian cancer with defects in DNA damage repair (DDR+).
Secondary Objectives:	**Secondary Endpoints:**
• To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging overall survival (OS) in patients with advanced ovarian cancer with defects in DNA damage repair (DDR+). • To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging PFS in patients with advanced ovarian cancer unselected for DDR status. • To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging OS in patients with advanced ovarian cancer unselected for DDR status. • To evaluate the effect on PFS and OS of platinum-based chemotherapy followed by talazoparib maintenance versus platinum-based chemotherapy	• OS in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS based on BICR assessment per RECIST v1.1 in patients unselected for DDR status. • PFS based on investigator assessment per RECIST v1.1 in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS2 based on investigator assessment in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS based on investigator assessment per Gynecological Cancer Intergroup (GCIG) criteria in patients with tumors that are DDR+ and in patients unselected for DDR status. • AEs (as graded by NCI CTCAE v4.03); laboratory abnormalities (as graded by NCI CTCAE v4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs). • PK parameters, including C_{trough} and C_{max} for avelumab and C_{trough} for talazoparib. • Anti-drug antibodies (ADA) and neutralizing

plus bevacizumab followed by bevacizumab maintenance in patients with advanced ovarian cancer with DDR+ and unselected for DDR status. • 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 avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance in Arm A as well as well as PK of talazoparib in combination with avelumab (Arm A) and as a single agent (Arm B). • To evaluate the immunogenicity of avelumab in Arm A (avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance). • To evaluate the effect of avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance and platinum-based chemotherapy followed by talazoparib maintenance versus platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance on patient reported outcome (PRO) including the assessments of disease-related symptoms, treatment side effects and health-related quality of life (HRQoL). • To assess the correlation of anti-tumor activity with PD-L1 expression, tumor mutational burden (TMB) and with potential biomarkers of PARP inhibitor sensitivity in baseline tumor tissue. • To assess the correlation of anti-tumor activity with TMB and potential biomarkers of PARP inhibitor sensitivity in baseline circulating tumor (ct) DNA.	antibody (NAb) against avelumab. • Disease related symptoms and treatment side effects as measured by the NCCN-FACT FOSI-18 and health-related quality of life (HRQOL) as measured by NCCN-FACT FOSI-18 and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L). • PD-L1 expression, TMB, genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue. • Assessment of defects in a panel of key oncogenes, including several considered critical to effective DDR and TMB in ctDNA at baseline.
CCI [redacted]	[redacted]

	CCI [redacted]

Study Design

This is a Phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of avelumab in combination with chemotherapy followed by maintenance therapy of avelumab in combination with the PARP inhibitor talazoparib in patients with previously untreated advanced ovarian cancer. Patients must meet full eligibility criteria as specified in Section 4.

The study design, including the number of patients to be randomized in each treatment arm, is illustrated in the study schematic figure below.

Approximately 720 patients (including 360 patients with tumors that are DDR+) who are candidates for frontline chemotherapy followed by maintenance were planned to be randomized in a 2.5:1:2.5 ratio stratified by germline BRCA 1/2 mutational status (gBRCA+ vs gBRCA-) and resection status (adjuvant with >1 mm and ≤1 cm residual disease vs adjuvant with >1 cm residual disease vs neoadjuvant) to one of the following treatment arms:

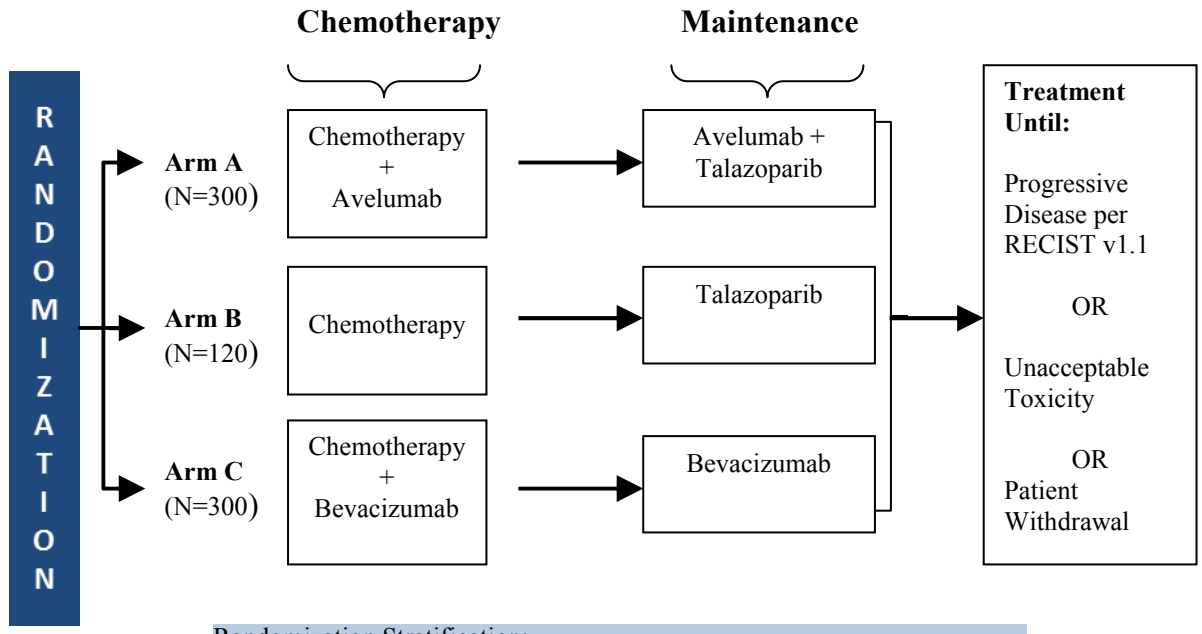
- Arm A: platinum-based chemotherapy + avelumab followed by avelumab + talazoparib maintenance;
- Arm B: platinum-based chemotherapy followed by talazoparib maintenance;
- Arm C: platinum-based chemotherapy + bevacizumab followed by bevacizumab maintenance.

No new patients could be screened or randomized as of 19 March 2019.

Intravenous carboplatin and paclitaxel will be used as the chemotherapy backbone, consisting of Q3W carboplatin and paclitaxel.

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 to be followed, upon recovery from surgery, by the remaining 3 cycles of chemotherapy.

Study Schematic



2.5:1:2.5

N = ~720

Randomization Stratification:

- germline BRCA 1/2 mutational status (gBRCA+ vs gBRCA-).
- Adjuvant with >1 mm and ≤1 cm residual disease vs. Adjuvant with >1 cm residual disease vs. Neoadjuvant.

gBRCA = germline BReast CAncer gene; N = number of patients.

Study Treatments

The study period includes two treatment periods, the chemotherapy period and the maintenance period. For the purpose of scheduling evaluations, providing clarity on assessments, and consistent on-treatment assessments across all three treatment arms, the definition of cycle length varies between the chemotherapy period and the maintenance period. In the chemotherapy period, a cycle is defined as 3 weeks (21 days), and due to the biweekly schedule of avelumab and the Q3W schedule for bevacizumab, a cycle in the maintenance period is defined as 6 weeks (42 days). See Section 1.2.5.1 for additional information.

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

Arm A:

- Paclitaxel 175 mg/m^2 intravenously (IV) over 3 hours followed by Carboplatin area under the curve (AUC) 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.

- Avelumab 800 mg administered intravenously on Day 1 of each 3-week cycle for 6 cycles.

Arm B:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.

Arm C:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5or 6 IV over 15-60 minutes on Day 1 of each 3-week cycle for 6 cycles.

- Bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle beginning with Cycle 2 for adjuvant patients (may begin with Cycle 1 if surgery completed >4 weeks prior to randomization and no contraindications), and for neoadjuvant patients, bevacizumab will be given on Day 1 of each 3-week cycle for Cycles 1, 2, 5, and 6.

For patients who are enrolled to undergo neoadjuvant chemotherapy with interval debulking surgery, the first 3 cycles of chemotherapy will be administered prior to interval debulking surgery. Patients will stay on study regardless of the surgery outcome (eg, extend of residual disease) and will receive the remaining 3 cycles of chemotherapy.

Patients who have to discontinue chemotherapy (carboplatin and paclitaxel) for unacceptable toxicities prior to the end of Cycle 6 may enter maintenance period, if deemed clinically acceptable by the investigator, and will receive avelumab and talazoparib (Arm A) or talazoparib (Arm B), or bevacizumab (Arm C).

Maintenance period should begin within 4 weeks of the last dose of chemotherapy. The first visit of maintenance therapy will be designated maintenance Cycle 1 Day 1 even if the last chemotherapy cycle was not completed.

For the **maintenance period** of the study, study drugs will be assigned and given as follows.

Arm A:

- Avelumab 800 mg administered intravenously on Days 1, 15, and 29 of each 6-week cycle in combination with talazoparib 0.75 mg self-administered orally once per day.

Arm B:

- Talazoparib 0.75 mg self-administered orally once a day, every day of each 6-week cycle.

Arm C:

- Bevacizumab 15 mg/kg administered intravenously on Days 1 and 22 of each 6-week cycle.

Effective with IRB/EC approval of amendment 2, patients will receive study treatment until progressive disease (PD) as assessed by the investigator, unacceptable toxicity, or withdrawal of consent, whichever is earliest. For avelumab and talazoparib, the maximum duration of maintenance treatment is 24 months. For bevacizumab, the maximum duration of treatment is 21 or 22 doses, per local approval, including the chemotherapy period. Patients who discontinue all study treatment and have PD based on investigator assessment will be followed for a 90-day Safety Follow-up Period.

Statistical Methods

As of 19 March 2019, the study was stopped for enrollment. Approximately 11% of the patients originally planned to be randomized in the study had been randomized. Therefore, no statistical hypotheses will be tested. Patient characteristics, treatment duration and safety endpoints will be summarized by treatment arm.

SCHEDULE OF ACTIVITIES (OBSOLETE)

Effective with IRB/EC approval of Amendment 2, the SOA below is no longer applicable. Please refer to Appendix 6 for the revised SOA.

The schedule of activities (SOA) tables below provide an overview of the protocol visits and procedures for each treatment arm. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. Patients who are enrolled prior to neoadjuvant therapy will undergo interval debulking surgery during the chemotherapy period as described in Section 5.10.2.1 and will resume on the schedule of assessments upon recovery.

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

Table 1. Schedule of Activities: Chemotherapy + Avelumab Followed by Avelumab + Talazoparib (Arm A)/Chemotherapy Followed by Talazoparib Alone (Arm B)—Obsolete

Protocol Activities[1]	Screening	On -Treatment						Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)					
	Within 28 Days Prior to Randomization	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[40]	Short-Term Follow-up (Day After Last Dose, 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow- up ±14 days[42]
Clinical Assessments										
Informed consent	X									
Medical/Oncological history[2]	X									
Physical examination[3]	X	X			X	X	X	X		
ECOG Performance Status[3]	X	X			X	X	X	X		
Blood Pressure, Temperature, Pulse Rate[4]	X	X			X	X	X	X		
Contraception Check[5]	X	X			X		X	X	X	

Table 1. Schedule of Activities: Chemotherapy + Avelumab Followed by Avelumab + Talazoparib (Arm A)/Chemotherapy Followed by Talazoparib Alone (Arm B)—Obsolete

Protocol Activities[1]	Screening	On -Treatment						Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)					
	Within 28 Days Prior to Randomization	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[40]	Short-Term Follow-up (Day After Last Dose, 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow- up ±14 days[42]
Laboratory Studies										
Hematology[6]	X	X			X	X	X	X	X (Day 30)	
Blood chemistry[6]	X	X			X	X	X	X	X (Day 30)	
Coagulation[6]	X	X			X			X		
CA-125[7]	X	X			X			X		
HBV and HCV[8]	X									
Thyroid Function/ACTH[9]	X	C2D1, C4D1, and C6D1 only			C1D1, then every 12 weeks thereafter			X		
Serum/Urine Pregnancy Test[10]	X	X			X		X	X		
Urinalysis[11]	X	X			X		X	X		
12-Lead Electrocardiogram (ECG)[12]	X				X (C1 only)			X		
Randomization/Study Treatment										
Blood sample for germline BRCA1/2 testing[13]	X									
Randomization[14]	X									
Paclitaxel/Carboplatin Administration[15]		X								
Talazoparib Administration[16]					QD					
Avelumab Administration[17]		X (Arm A only)			X (Arm A only)	X (Arm A only)	X (Arm A only)			
Disease Assessments										
Tumor Assessments (including scans)[19]	X	At 9 and 18 weeks after date of randomization, then every 12 weeks thereafter until PD by BICR regardless of initiation of new anti-cancer therapy								

Table 1. Schedule of Activities: Chemotherapy + Avelumab Followed by Avelumab + Talazoparib (Arm A)/Chemotherapy Followed by Talazoparib Alone (Arm B)—Obsolete

Protocol Activities[1]	Screening	On -Treatment						Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)					
	Within 28 Days Prior to Randomization	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[40]	Short-Term Follow-up (Day After Last Dose, 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow- up ±14 days[42]
Other Clinical Assessments										
Serious and non-serious adverse event monitoring[20]	X	Monitored and recorded throughout treatment						X	X	
Concomitant Treatment(s)[21]	X	Monitored and recorded throughout treatment						X	X	
Patient-Reported Outcomes (NFOSI-18)[22]		Weekly in the first 3 cycles, and then Day 1 of every subsequent cycle			X			X	Every 6 weeks for 3 years from randomization	
Patient Global Impression of Severity (PGI-S)[23]		Weekly in the first 3 cycles						X		
Patient Global Impression of Change (PGI-C)[24]		Days 8 and 15 of Cycle 1, and then Days 1, 8, 15 of Cycles 2 and 3						X		
Patient-Reported Outcomes (EQ-5D-5L)[25]		X			X			X	Every 6 weeks for 3 years from randomization	
CCI [redacted]		[redacted]						[redacted]	[redacted]	
Other Samplings										
Blood for Avelumab ADA (Immunogenicity) Testing[27]		X (C1-C4 only, Arm A only)			X (C1, 2, 4, 6, 10, Arm A only)		X (C1, Arm A only)	X		
Blood sampling for Talazoparib Pharmacokinetics[28]					X (C1 only)	X (C1 only)	X (C1 only)			
Blood Sampling for Avelumab Pharmacokinetics[29]		X (C1-C4 only, Arm A only)			X (C1, 2, 4, 6, 10, Arm A only)		X (C1, Arm A only)	X		

Table 1. Schedule of Activities: Chemotherapy + Avelumab Followed by Avelumab + Talazoparib (Arm A)/Chemotherapy Followed by Talazoparib Alone (Arm B)—Obsolete

Protocol Activities[1]	Screening	On -Treatment						Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)					
	Within 28 Days Prior to Randomization	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[40]	Short-Term Follow-up (Day After Last Dose, 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow- up ±14 days[42]
Mandatory Archival FFPE Tumor Tissue Block or *De Novo* Tumor Biopsy[30]	X									
Optional *De Novo* Tumor Biopsy[31]								X		
Genomic banked biospecimens Prep D1[32]		X (C1 only)								
Blood Biospecimen for DNA[33]		X (C1 only)								
Plasma for circulating tumor (ct)DNA analysis[34]	X	X (C1 and C2 only)			X (C1 only)	X (C1 only)		X		
Plasma for Biomarker/Proteomic/ Metabolomic Analysis[35]		X (C1 only)			X (C1 only)	X (C1 only)		X		
Serum for Biomarker/Proteomic/ Metabolomic Analysis[36]		X (C1 only)			X (C1 only)	X (C1 only)		X		
CCI [redacted]		[redacted]			[redacted]	[redacted]		[redacted]		
Blood Draw for RNA analysis[38]		X (C1 only)								

Table 2. Schedule of Activities: Chemotherapy + Bevacizumab Followed by Bevacizumab (Arm C)—Obsolete

Protocol Activities[1]	Screening	On -Treatment					Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)				
	Within 28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 22 (±3 days)	End of Treatment/ Withdrawal[40]	Short-Term Follow-up (Day After Last Dose 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow-up ±14 days[42]
Informed consent	X								
Medical/Oncological history[2]	X								
Physical examination[3]	X	X			X	X	X		
ECOG Performance Status[3]	X	X			X	X	X		
Blood Pressure, Temperature, Pulse Rate[4]	X	X			X	X	X		
Contraception Check[5]	X	X			X	X	X	X	
Laboratory Studies									
Hematology[6]	X	X			X	X	X		
Blood chemistry[6]	X	X			X	X	X		
Coagulation[6]	X	X			X		X		
CA-125[7]	X	X			X		X		
HBV and HCV[8]	X								
Thyroid Function/ACTH[9]	X	C2D1, then every other cycle thereafter			C1D1, then every 12 weeks thereafter		X		
Serum/Urine Pregnancy Test[10]	X	X			X	X	X		
Urinalysis[11]	X	X			X	X	X		
12-Lead ECG[12]	X				X (C1 only)		X		
Randomization/StudyTreatment									
Blood sample for germline BRCA1/2 testing[13]	X								
Randomization[14]	X								
Paclitaxel/Carboplatin Administration[15]		X							
Bevacizumab Administration[18]		X			X	X			

Table 2. Schedule of Activities: Chemotherapy + Bevacizumab Followed by Bevacizumab (Arm C)—Obsolete

Protocol Activities[1]	Screening	On -Treatment					Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)				
	Within 28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 22 (±3 days)	End of Treatment/ Withdrawal[40]	Short-Term Follow-up (Day After Last Dose 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow-up ±14 days[42]
Disease Assessments									
Tumor Assessments (including scans)[19]	X	At 9 and 18 weeks after date of randomization, then every 12 weeks thereafter until PD by BICR regardless of initiation of new anti-cancer therapy							
Other Clinical Assessments									
Serious and non-serious adverse event monitoring[20]	X	Monitored and recorded throughout treatment					X	X	
Concomitant Treatment(s)[21]	X	Monitored and recorded throughout treatment					X	X	
Patient-Reported Outcomes (NFOSI-18)[22]		Weekly in the first 3 cycles, and then Day 1 of every subsequent cycle			X		X	Every 6 weeks for 3 years from randomization	
Patient Global Impression of Severity (PGI-S)[23]		Weekly in the first 3 cycles					X		
Patient Global Impression of Change (PGI-C)[24]		Days 8 and 15 of Cycle 1, and then Days 1, 8, 15 of Cycles 2 and 3					X		
Patient-Reported Outcomes (EQ-5D-5L)[25]		X			X		X	Every 6 weeks for 3 years from randomization	
CCI [redacted]		[redacted]			[redacted]		[redacted]	[redacted]	
Other Samplings									
Mandatory Archival FFPE Tumor Tissue Block or *De Novo* Tumor Biopsy[30]	X								
Optional *De Novo* Tumor Biopsy[31]							X		
Genomic banked biospecimens Prep D1[32]		X (C1 only)							
Blood Biospecimen for DNA[33]		X (C1 only)							

Table 2. Schedule of Activities: Chemotherapy + Bevacizumab Followed by Bevacizumab (Arm C)—Obsolete

Protocol Activities[1]	Screening	On -Treatment					Post Treatment Period		
		Chemotherapy Period (1 cycle = 3 weeks = 21 days)			Maintenance Period[39] (1 cycle = 6 weeks = 42 days)				
	Within 28 Days Prior to Randomization	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 22 (±3 days)	End of Treatment/ Withdrawal[40]	Short-Term Follow-up (Day After Last Dose 30, 60, and 90 ±3 days)[41]	Survival and Long-Term Follow-up ±14 days[42]
Plasma for circulating tumor (ct)DNA analysis[34]	X	X (C1 and C2 only)			X (C1 only)	X (C1 only)	X		
Plasma for Biomarker/Proteomic/ Metabolomic Analysis[35]		X (C1 only)			X (C1 only)		X		
Serum for Biomarker/Proteomic/ Metabolomic Analysis[36]		X (C1 only)			X (C1 only)		X		
CCI [redacted]		[redacted]			[redacted]		[redacted]		
Blood Draw for RNA analysis[38]		X (C1 only)							

Footnotes for Schedule of Activities Tables

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 periods.
2. **Medical/Oncological History**: Both medical and oncological histories are to be collected within 28 days prior to first dose of study treatment. Medical history should include history of other disease (active or resolved) as well as concomitant illnesses. Oncological history should include information on surgery and radiation therapy.
3. **Physical Examination**: Includes an examination of major body systems, assessment of ECOG performance status, and weight (height included at screening only). Weight will not be collected at End of Treatment. See Section 7.1.5.
4. **Blood Pressure, Temperature, Pulse Rate**: See Section 7.1.5.
5. **Contraception Check**: Only for patients who are of child-bearing potential. See Section 4.3 and Section 7.1.2.
6. **Hematology, Blood Chemistry, and Coagulation**: Cycle 1 Day 1 tests do not need to be repeated if they have been conducted in the prior 3 days. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. Required tests are listed in Section 7.1.4. Hematology and Blood Chemistry must be performed at screening, Cycle 1 Day 1 (unless done in the prior 3 days), and on Day 1, Day 15 and Day 29 of each maintenance cycle, End of Treatment, and at Day 30 during the follow-up for patients in Arm A & B. Hematology and Blood Chemistry must be performed at screening, Cycle 1 Day 1, and on Days 1, and 22 of each maintenance cycle, and end of treatment in Arm C. Coagulation and hematology are required as noted in this table. Any test may also be performed when clinically indicated.

7. **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. Rising CA-125 levels alone will not be considered evidence of progression.
8. **HBV and HCV Tests**: HBV surface antigen and anti-HCV antibody will be performed at Screening. HCV RNA will be performed if anti-HCV antibody test is positive (see Section 7.1.4 and Table 12).
9. **Thyroid Function Tests and ACTH**: Baseline free T4, TSH, and ACTH will be performed. Additional tests will be performed at every other cycle. See Section 7.1.4.
10. **Serum/Urine Pregnancy Test**: For women of childbearing potential, a serum or urine pregnancy test must be performed at screening, on Day 1 of each chemotherapy cycle, on Day 1 and Day 29 (Arms A and B) and Day 1 and Day 22 (Arm C) of each maintenance cycle, and at the end of study treatment. The pregnancy test should be repeated if 1 menstrual cycle is missed or if the potential of pregnancy is otherwise suspected. See Section 7.1.1.
11. **Urinalysis:** See Section 7.1.4.
12. **12 lead ECG**: See Section 7.1.6 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 prior to start of treatment on Cycle 1 Day 1 and at end of treatment/withdrawal of the maintenance period (all arms). Additional ECGs will be performed as clinically indicated. Clinically significant findings seen on follow-up ECGs should be recorded as adverse events.
13. **Blood Sample for Germline BRCA1/2 Testing (10 mL)**: Results are to be used for designation of BRCA1/2 defect status and subsequent stratification during the randomization process. See Section 6.1. For patients with an existing test result for germline BRCA 1/2 defect status, test result must have been obtained using a CLIA (or comparable local validation) approved assay.
14. **Randomization:** Patients meeting all entry criteria will be randomized using the Interactive Response Technology system. See Section 5.1. Study treatment must start within 3 days after randomization.
15. **Paclitaxel/Carboplatin Administration:** Paclitaxel 175 mg/m2 IV, followed by carboplatin dose AUC 5 or AUC 6 IV on Day 1 of every chemotherapy cycle as described in Section 5.4. Premedication will be administered as specified in Section 5.4.1.1. On visits when chemotherapy is administered in combination with avelumab or bevacizumab (Day 1 of each 21-day cycle), chemotherapy will be infused before either avelumab or bevacizumab. See Section 5.4.2 and Section 5.4.3. See Section 6.2 for guidance on treatment duration.
16. **Study Treatment Talazoparib (Arms A and B, Maintenance Period Only)**: Talazoparib will be self-administered orally once per day at 0.75 mg and will continue through end of Maintenance treatment. On Days 1, 15, and 29 of each Maintenance cycle, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and for patients randomized to Arm A, before the avelumab infusion. See Section 6.2 for guidance on treatment duration.
17. **Study Treatment Avelumab (Arm A Only):** Patients will receive avelumab 800 mg administered on Day 1 of each 3-week cycle intravenously *after* administration of paclitaxel and carboplatin during the chemotherapy period. During the maintenance period patients will receive avelumab 800 mg administered once every 2 weeks *after* dosing with talazoparib on Days 1, 15, and 29 of each 6-week maintenance cycle. See Section 6.2 for guidance on treatment duration.
18. **Study Treatment Bevacizumab (Arm C Only):** Patients will receive bevacizumab 15mg/kg administered once every 3 weeks intravenously on Day 1 of Cycle 2, 3, 4, 5, and 6 of chemotherapy (may begin with cycle 1 if surgery completed >4 weeks prior to randomization and no contraindications) for adjuvant patients, and on Day 1 of Cycles 1, 2, 5, and 6 for neoadjuvant patients. During Maintenance, bevacizumab will be administered once every 3 weeks intravenously on Days 1 and 22 of each cycle. See Section 6.2 for guidance on treatment duration.
19. **Tumor Assessments**: Tumor assessment must be performed at screening, at 9 and 18 weeks (±3 days) from date of randomization, and every 12 weeks thereafter until PD by BICR regardless of initiation of new anti-cancer therapy. For patients who undergo interval debulking surgery (IDS), an additional tumor assessment should be performed after surgery. All radiographic images will be collected and may be objectively verified by an independent third party core imaging laboratory as described in Imaging Manual. See Section 7.6 for additional detailed information.
20. **Adverse Events**: Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. See Section 8.1.4 for guidance on the time period for collecting and reporting AE and SAEs.

21. **Concomitant Medications/Treatments**: Concomitant medications and treatments 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, the end of treatment/withdrawal visit or the end of the safety follow-up period, whichever is later. See Section 5.10 for further details.
22. **NFOSI-18**: All patients will complete the self-administered questionnaire electronically on Day 1, 8 and 15 of the first 3 cycles and then Day 1 of subsequent cycles in the chemotherapy period, on Day 1 of every cycle in the maintenance period, at the EOT/Withdrawal visit, and every 6 weeks during the post treatment and survival follow-up period for a total of 3 years from the date of patient randomization.
23. **PGI-S**: Patients enrolled in the US who are fluent in English will complete this 1 item electronically at Days 1, 8 and 15 of cycles 1, 2, and 3 in the chemotherapy period and at EOT/Withdrawal visit.
24. **PGI-C:** Patients enrolled in the US who are fluent in English will complete this 1 item electronically at Days 8 and 15 of Cycle 1 and Days 1, 8, and 15 of Cycles 2 and 3 in the chemotherapy period and at EOT/Withdrawal visit.
25. **EQ-5D-5L**: All patients will complete the self-administered questionnaire electronically on Day 1 of every chemotherapy cycle, on Day 1 of every cycle in the maintenance period, at the EOT/Withdrawal visit, and every 6 weeks during the post treatment and survival follow-up period for a total of 3 years from the date of patient randomization.

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27. **Blood for Avelumab Immunogenicity (Arm A only):** Testing (anti-avelumab antibodies; anti-drug antibodies [ADAs], neutralizing anti-avelumab antibodies [NAbs]): All immunogenicity samples (3.5 mL whole blood) should be collected pre-dose and within 2 hours before the start of the avelumab infusion.

    Chemotherapy Period: Immunogenicity sample (3.5 mL whole blood) will be collected predose on Day 1 of chemotherapy Cycles 1-4.
    Maintenance Period: Immunogenicity samples (3.5 mL whole blood) will be collected predose on Days 1 and 29 of maintenance Cycle 1. Thereafter, immunogenicity samples will be collected predose on Day 1 of maintenance cycles 2, 4, 6, 10 and at the end of treatment. All samples that are positive for ADA will also undergo characterization for NAb. See Section 7.3.
28. **Blood sampling for Talazoparib Pharmacokinetics (Arms A and B):** PK samples (3.0 mL whole blood) will be collected pre-dose on Days 1, 15, and 29 of Cycle 1 of maintenance treatment.
29. **Blood Sampling for Avelumab Pharmacokinetics for all patients receiving avelumab (Arm A Only**):

    Chemotherapy Period: PK samples (3.5 mL whole blood) for avelumab will be collected within 2 hours prior to and at the end of infusion (within 10 minutes after the avelumab infusion ends) on Day 1 of Cycles 1-4.

    Maintenance Period: Pre-dose PK samples (3.5 mL whole blood) for avelumab will be collected within 1 hour prior to taking talazoparib dose and the post-dose avelumab PK sample should be taken within 10 minutes after the avelumab infusion ends on Days 1 and 29 of the first maintenance cycle. Thereafter, PK samples will be collected pre-dose within 1 hour prior to taking talazoparib dose and the post-dose avelumab PK samples should be taken within 10 minutes after the avelumab infusion ends on Day 1 of maintenance Cycles 2, 4, 6, 10 and at the end of treatment. Details are provided in Section 7.2.1.
30. **Mandatory FFPE Tumor Tissue**: A mandatory formalin-fixed, paraffin-embedded (FFPE) tumor tissue block sufficient in size to allow for sectioning of a minimum of twenty-five (25) 5-micron tissue sections must be submitted during screening. If no appropriate archive tissue is available, a *de novo* (ie, fresh) tumor sample must be obtained in accord with local institutional practice for tumor biopsies. If an FFPE tumor tissue block cannot be provided, due to documented local/institutional regulations, sites should provide a minimum of 25 unstained slides as detailed in Section 7.4.1. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.
31. **Optional *De Novo* Tumor Biopsy**: An optional *de novo* (ie, fresh) tumor core biopsy, to provide a FFPE tumor tissue block, is requested to be collected at End of Treatment. If an FFPE tumor tissue block cannot be provided, due to documented local/institutional regulations, sites are requested to provide at least fifteen (15) unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material), is not adequate and should not be submitted.

32. **Genomic Banked Biospecimen Prep D1**: A 4 mL blood sample will be collected on Day 1 of Cycle 1 of chemotherapy prior to dosing and retained in a biobank for possible pharmacogenomic assessments, unless prohibited by local regulations or by decision of the IRB or EC. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a patient visit.
33. **Blood Draw for DNA Analysis**: A 4 mL whole blood biospecimen will be collected prior to dosing on Day 1 of chemotherapy Cycle 1.
34. **Plasma for ctDNA**: A 20 mL blood specimen will be collected at screening and prior to dosing on Day 1 of chemotherapy Cycles 1 and 2 (all Arms), on Day 1 of maintenance cycle 1 (all arms), on day 15 (Arms A and B only) and day 22 (Arm C only) of maintenance Cycle 1, and at EOT of maintenance treatment.
35. **Plasma for Biomarker/Proteomic/Metabolomic Analysis**: A 4 mL blood biospecimen will be collected prior to dosing on Day 1 of Cycle 1 of chemotherapy and of maintenance treatments (all arms), Day 15 of Cycle 1 maintenance (Arms A and B) and at EOT.
36. **Serum for Biomarker/Proteomic/Metabolomic Analysis**: A 10 mL blood biospecimen will be collected prior to dosing on Day 1 of Cycle 1 of chemotherapy and of maintenance treatments (all arms), Day 15 of Cycle 1 maintenance (Arms A and B) and at EOT.

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38. **Blood Draw for RNA Analysis**: Two 2.5 mL whole blood samples will be collected in designated tube to optimize sample for RNA analysis prior to dosing on Day 1 of Cycle 1 of chemotherapy treatment (all arms).
39. **Maintenance Period**: Maintenance period should begin within 4 weeks after the last dose of chemotherapy.
40. **End of Treatment/Withdrawal**: Performed when criteria for treatment discontinuation are met. 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. See Section 6.4.
41. **Short-Term Follow-up**: All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first. See Section 6.5 for guidance on tumor assessment during follow-up.
42. **Long-Term/Survival Follow up**: Following completion of the initial 90-day short-term follow-up period, all patients will be followed for survival and subsequent anti-cancer treatments and for diagnosis of myelodysplastic syndrome or acute myeloid leukemia every 12 weeks (±14 days) until death, end of study, or patient withdrawal of consent, whichever occurs first. See Section 6.5 for guidance on tumor assessment during follow-up.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

1.1.1. Avelumab

Avelumab is an immunoglobulin-G1 (IgG1) monoclonal antibody (mAb) directed against PD-L1. Avelumab selectively binds to PD-L1 and competitively blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumor T-cell responses. For complete details of the in vitro and nonclinical studies, refer to the Investigator's Brochure (IB) for avelumab.

Additional information for avelumab may be found in the single reference safety document (SRSD), which for this study is the IB for avelumab.[1]

1.1.2. Talazoparib

Talazoparib is a potent, orally bioavailable PARP inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise DNA repair, an effect referred to as synthetic lethality, by inhibiting PARP catalytic activity and trapping PARP protein on DNA, thereby preventing DNA repair, replication, and transcription.[2,3,4]

PARP inhibitors including talazoparib exert cytotoxic effects by 2 mechanisms:

- In cell-free enzyme assays, talazoparib inhibited PARP1 and PARP2 catalytic activity with inhibitory constant (K_i) values of 1.2 nM and 0.87 nM, respectively.[5] Talazoparib was 3.4- to 8.3-fold more potent than other PARP inhibitors that are in clinical development, veliparib, rucaparib, and olaparib.[6]

- In addition to inhibition of PARP catalytic activity, talazoparib also promotes cell toxicity by trapping PARP protein on DNA, which prevents DNA repair, replication, and transcription.[2,3,4]

Although other PARP inhibitors also possess both activities, in vitro studies demonstrated that talazoparib has more potent PARP trapping activity than other PARP inhibitors that have been approved and/or in clinical development.[4,7]

DNA damage promotes inflammation via the NF-κB pathway[8] and the stimulator of interferon genes (STING) pathway,[9,10] and has been shown to increase the intrinsic immunogenicity of tumor cells via up regulation of major histocompatibility complex (MHC), natural killer group 2 member D Ligand (NKG2DL), and inducible costimulator ligand (ICOSL).[11,12] As such, increased DNA damage via PARP inhibition is expected to enhance effective recognition and infiltration of tumors by immune cells. In keeping with this expectation, talazoparib has been shown to promote T-cell and natural killer (NK) cell infiltration and activation in a mouse model of ovarian cancer.[13] Additionally, talazoparib treatment has been shown to lead to increased expression of PD-L1 by tumor cells,[14] suggesting that this may represent a means by which tumors function to inhibit talazoparib

mediated anti-tumor immunity, and that the combination of talazoparib and anti PD-L1 may further enhance anti-tumor activity. This hypothesis is supported by preclinical studies in a syngeneic model of breast cancer, which have demonstrated increased tumor growth inhibition for an alternative PARP inhibitor, olaparib, when used in combination with an anti-PD-L1 antibody.[14]

Additional information for talazoparib may be found in the SRSD, which for this study is the IB for talazoparib.[15]

The SRSD for the comparator agent, bevacizumab is the Summary of Product Characteristics (SmPC).[16]

1.2. Background and Rationale

On 21 December 2018, the Sponsor (Pfizer and Merck KGaA) announced that the Phase 3 JAVELIN Ovarian 100 study (B9991010) was stopped due to futility of efficacy at a planned interim analysis in alignment with the recommendation of both the Independent Data Monitoring Committee and the Protocol Steering Committee. There were no new safety signals identified from the B9991010 study relative to the known safety profile of avelumab or the other study medications.

Detailed analyses of the data from study B9991010 have since been performed to determine the impact on the ongoing JAVELIN Ovarian PARP 100 study (B9991030). Although the overall safety profile of avelumab remains unchanged, the lack of efficacy with avelumab in the treatment of frontline ovarian cancer observed in study B9991010 reduces the probability of technical success of study B9991030 and of regulatory success of any submission based on this study.

In addition, the recent approvals in the United States and in the European Union of a PARPinhibitor in the front-line maintenance setting based on the practice-changing results from the SOLO-1 trial (National Clinical Trial # 01844986) provide a sound rationale for PARP inhibitor therapy instead of bevacizumab for patients with deleterious germline or somatic BRCA mutations. This new treatment paradigm creates a recruitment challenge for enrolling BRCA+ patients into the B9991030 study along with a risk for high attrition of BRCA+ patients when randomized to the bevacizumab control arm.

Therefore, based on the totality of the information, the Sponsor made the decision to stop enrollment in the B9991030 study. On 19 March 2019, a Dear Investigatior Letter was issued to notify the investigational sites that no new patients could be screened or randomized.

Patients who had been randomized prior to 19 March 2019 were able to remain in the study provided they sign the Informed Consent Addendum upon its approval by local institutional review board (IRB)/ethics committee (EC). Patients who remain in the study will continue receiving investigational products according to their randomized treatment assignment and will be monitored for appropriate safety assessments until treatment discontinuation.

1.2.1. Ovarian Cancer

Ovarian cancer is the leading cause of death from gynecologic cancer and the fifth most common cause of cancer mortality in women. 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.[27] Although expectations for long-term survival can be high if the cancer is identified and treated early, the 5-year survival rate for women diagnosed with advanced ovarian cancer is less than 30% from statistics in the United States and less than 20% in the United Kingdom.[28,29]

Ovarian neoplasms consist of several histopathological entities. Epithelial ovarian cancer (EOC) comprises the majority of malignant ovarian neoplasms (about 80%)[30] however, other less common pathologic subtypes must be considered in treatment recommendations, eg, fallopian tube cancer (FTC) and primary peritoneal cancer (PPC) which are less common neoplasms, are managed in a similar manner to EOC.

Carboplatin in combination with paclitaxel is the current standard of care in the front-line EOC treatment setting. Complete response is achieved in approximately 75% of patients, but the median progression-free survival (PFS) is approximately 18 months and most patients ultimately succumb to the disease.[30] 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.

Several studies have been conducted in the frontline treatment setting. Due to long post-progression survival and the potential for post-treatment crossover to confound overall survival (OS) results interpretation, PFS is an accepted endpoint in this setting.[31] Bevacizumab (Avastin®, Genentech, Inc.) in combination with chemotherapy followed by maintenance therapy (16 cycles or 48 weeks in GOG-218 study, 12 cycles or 36 weeks in ICON 7 study) demonstrated improvement in PFS in the front-line treatment setting[32,33] but without statistically significant improvement on OS.[35] Both trials focused on patients who were at high-risk for recurrence; ICON 7 allowed Stage I and II patients considered high risk for recurrence (high-grade), whereas GOG-218 included only patients with Stage III and IV disease. In ICON 7, 31% of patients had Federation of Gynecology and Obstetrics (FIGO) Stage III or IV disease and >1 cm residual disease after debulking surgery and in GOG-218, 66% of patients had Stage III and >1 cm residual disease or Stage IV. Bevacizumab is currently approved in the frontline, platinum-sensitive recurrent setting, and platinum-resistant recurrent treatment settings in the European Union (EU)[57] while in the United States (US), it is approved in the platinum-sensitive recurrent and platinum-resistant treatment setting. Despite this lack of approval in the US, bevacizumab is routinely used both in the US and EU in the frontline setting. Subsequent to the original protocol, on June 13, 2018, the FDA approved bevacizumab for use in the frontline setting.[58]

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.[36] A randomized study demonstrated non-inferiority of this approach with respect to overall survival compared to adjuvant therapy in high-risk patients.[21] 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.[31] A number of frontline studies have successfully enrolled patients undergoing either adjuvant or neoadjuvant therapies in the same trial (GOG-262 and ICON 8). ICON 8 results comparing neoadjuvant and adjuvant treatment are pending. The primary analysis of GOG-262 was published in 2016.[32] In GOG-262, the primary research question was whether dose dense paclitaxel could improve outcome in incompletely resected Stage III or IV disease. Both neoadjuvant and adjuvant were (pre-specified) treatment options, as well as the addition of bevacizumab. The primary endpoint was not met. Dose dense paclitaxel was not superior to the every 3 weeks (Q3W; standard) paclitaxel regimen. A pre-specified subgroup analysis showed that in the absence of bevacizumab, there was a benefit for dose dense paclitaxel (median PFS [mPFS] 14.2 months versus 10.3 months, hazard ratio 0.62, 95% confidence interval [CI]: 0.40, 0.95, p=0.03). In the presence of bevacizumab, there was no difference in mPFS (14.9 versus 14.7 months).

The current standard of care in the frontline maintenance treatment setting is region-dependent. A significant number of patients, especially those with poor prognostic factors (incompletely resected Stage III and Stage IV), receive bevacizumab in combination with induction chemotherapy followed by bevacizumab maintenance therapy in regions where bevacizumab is available in this setting. For others, especially those with fewer poor prognostic factors, a standard of care option includes platinum doublet chemotherapy followed by best supportive care/observation or participation in a clinical trial.

For patients with Stage III and IV ovarian cancer, 80-85% will experience recurrent disease.[37] Depending on the time to recurrence (more or less than 6 months after last treatment), treatment options include retreatment with platinum containing therapy if recurrence occurs after more than 6 months (‘platinum sensitive recurrent disease’), and a variety of chemotherapy agents (eg, pegylated liposomal doxorubicin (PLD, topotecan, gemcitabine, weekly paclitaxel) if the recurrence occurs within 6 months (‘platinum resistant recurrent disease’). For patients who have not previously received bevacizumab, this agent can be added to the treatment. Newer treatment options include the addition of PARP inhibitor. Prognosis remains poor in the recurrent setting with approximately a median OS of 2-2.5 years for platinum sensitive recurrent disease. Prognosis for patient with platinum resistant disease is worse with a median OS of approximately 1 year.

1.2.2. Clinical Experience with Avelumab

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono and is indicated in the US for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC) and in adult patients having urothelial carcinoma (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Avelumab has been approved in the EU, Switzerland, Japan and Australia, and Israel for the treatment of MCC. Avelumab also is being studied in a wide variety of cancers, including non-small cell lung cancer (NSCLC), gastric cancer, renal cell carcinoma (RCC), ovarian cancer, UC, Hodgkin lymphoma, squamous cell cancer of the head and neck (SCCHN), and relapsed or refractory diffuse B-cell lymphoma, as a single agent or in combination with chemotherapy,

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

As of 09 June 2016, 53 patients were treated in the dose escalation phase of the EMR100070-001 study, with 4, 13, 15, and 21 patients treated with avelumab doses of 1, 3, 10, and 20 mg/kg Q2W, respectively. None of the patients treated with doses up to 10 mg/kg experienced a dose limiting toxicity (DLT), and the 10 mg/kg dose of avelumab was thus considered a safe and well tolerated dose for further investigation in the dose expansion cohorts. One DLT (a Grade 3 immune related adverse event characterized by increased creatine kinase, myositis, and myocarditis) was observed in 1 patient at the dose of 20 mg/kg.

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

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

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

Treatment-related TEAEs were observed in 1164 (67.0%) patients, and the most frequent (≥5%) were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%).

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

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

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

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

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

Infusion Related Reactions (IRRs): a total of 439 patients (25.3%) experienced at least 1 IRR, defined as a TEAE coded under the preferred terms of infusion related reaction, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, and abdominal pain according to a predefined case definition. The most common preferred terms that met the definition for an IRR included: infusion related reaction (17.0%), chills (5.4%), and pyrexia (3.6%). Most of the events were of Grade 1 or Grade 2 severity. Grade ≥3 IRRs occurred in 12 patients (0.7%) including 3 patients (0.2%) who experienced Grade 4 IRRs. No Grade 5 IRRs were reported. In most cases, the first occurrence of an IRR was related to the first infusion, with only 6 patients experiencing the first IRR at the fifth or later infusion. All Grade ≥3 IRRs

occurred with the first (7 patients) or second (5 patients) infusion. Overall, 21.6% of patients had 1 IRR, 2.6% of patients had 2 IRRs, 14 patients (0.8%) had 3 IRRs, and 3 patients had >3 IRRs. IRR recurrence after the fourth infusion was rare (15 patients) and all recurrent IRRs were of Grade 1 or 2 severity. In 35 patients (2.0%), treatment was permanently discontinued because of an IRR.

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

1.2.2.1. Clinical Experience From Study EMR 100070-001 in Patients with Ovarian Cancer

Study EMR 100070-001 evaluated avelumab in two cohorts of patients with ovarian cancer. The efficacy analysis of the ovarian cancer expansion cohort had a data cut-off of 31 December 2016. The ovarian cancer expansion cohort enrolled and treated a total of 125 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. All patients had a minimum follow-up time of 15 months, and 5 patients (4.0%) were still on treatment at the time of the cut-off for the analysis.

Table 3 presents the best overall response (BOR) results of 125 patients in the ovarian cancer expansion cohort, together with the objective response rate (ORR) according to RECIST 1.1, defined as the proportion of patients with a BOR of confirmed partial response (PR) or complete response (CR). The BOR for 9 patients (7.2%) were non-evaluable. The reasons for non-evaluable tumor response results included data missing or not assessable. The ORR based on confirmed responses for patients treated in the ovarian cancer expansion cohort, was 10.4% (13 of 125 patients). In 6 of the 13 responders (46.2%), the responses were ongoing at the time of the data cut-off. The onset of the response occurred at the time of the first assessment (~6 weeks) in 6 patients.

The median PFS for the ovarian cancer expansion cohort was 2.63 months (95% CI: 1.41, 2.76 months).

Table 3. Confirmed Tumor Response Observed in Ovarian Cancer Expansion Cohort

BOR by RECIST 1.1 (Confirmed)	Ovarian Cancer Expansion Cohort (N=125)
Complete Response, n (%)	2 (1.6)
Partial Response, n (%)	11 (8.8)
Stable Disease, n (%)	53 (42.4)
Progressive Disease, n (%)	50 (40.0)
Non-Evaluable [a], n (%)	9 (7.2)
ORR, n(%), (95% CI)	13 (10.4), (5.7, 17.1)

Source: Pfizer/Merck KGaA data on file, cut-off 31 December 2016.
BOR = best overall response; CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.
Objective response rate was defined as proportion of patients with BOR of CR or PR.
[a.] Non-evaluable includes 'missing' and 'not assessable'.

1.2.2.2. Safety of Avelumab Combined with Carboplatin and Paclitaxel in Ovarian Cancer Patients

The induction regimen as proposed for Arm A is similar to the regimen in Arm C (concurrent avelumab-carboplatin-paclitaxel) in the ongoing study B9991010. In study B9991010, 998 patients were randomized and 991 received at least one dose of study treatment including 329 patients who were treated in Arm C. On 14 December 2018, the external Data Monitoring Committee (eDMC) made the recommendation to terminate the B9991010 study due to futility of efficacy at a pre-planned interim analysis. However, there were no new safety signals identified from the B9991010 study relative to the known safety profile of avelumab or the other study medications.

1.2.2.3. Pharmacokinetics of Avelumab in Humans

Available pharmacokinetic (PK) data from Study EMR100070-001 show that the concentration at the end of the dosing interval (C_{trough}) increased more than proportionally to dose between 1 to 10 mg/kg, and proportionally to dose for doses above 10 mg/kg. The terminal half-life ($t_{1/2}$) also increased with dose; however, the geometric mean values for $t_{1/2}$ were similar for the 10 mg/kg and 20 mg/kg dose levels, at 94.6 hours (3.96 days) and 99.1 hours (4.1 days), respectively. This PK characteristic suggests that target-mediated drug disposition is involved in the clearance of avelumab, and that high PD-L1 target receptor occupancy (TO) is likely achieved throughout the dosing interval at doses of 10 mg/kg and 20 mg/kg given Q2W.

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

in the 3 mg/kg dose group. For the purposes of the current study, a fixed dosing strategy will be used for avelumab as described below in Section 1.2.5.1.

Avelumab is eliminated by intracellular lysosomal proteolytic degradation throughout the entire body and therefore is not expected to be affected by small molecule drugs that are cytochrome P450 (CYP450) enzyme modulators or by transporter modulators. Furthermore, avelumab itself is not expected to interfere with either absorption or elimination of small molecule drugs that are substrates of transporters, are metabolized via CYP450, hydrolysis or conjugation, and/or are renally excreted. Therefore, on this study there is very low potential for a drug-drug interaction (DDI) between avelumab and talazoparib, which is a small molecule cleared primarily via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation.

Population PK analysis did not show any meaningful effects on clearance of avelumab from premedication with acetaminophen (paracetamol) or diphenhydramine, nor from concomitant medication with ibuprofen, acetylsalicylic acid, opioids, corticosteroids, and biological therapies evaluated to date.

1.2.3. Clinical Experience with Talazoparib

Talazoparib is a potent, orally bioavailable, small molecule PARP inhibitor in development for the treatment of a variety of human cancers.

As of 30 November 2016, approximately 439 patients have received talazoparib in company sponsored studies in hematologic malignancies and solid tumors. Studies in solid tumors include a Phase 1 study (PRP-001) in advanced or recurrent solid tumors, a Phase 1 study in advanced malignancies (PRP-002), a Phase 2 study (673-201) in locally advanced and/or metastatic breast cancer patients with a germline BRCA defect, a Phase 3 study (673-301) in locally advanced or metastatic breast cancer with a germline BRCA defect, a Phase 1 hepatic impairment study (MDV3800-02), a Phase 1 absorption, distribution, metabolism and excretion (ADME) study (MDV3800-03) and a Phase 1 study on cardiac repolarization (MDV3800-14).

As of 30 November 2016, aggregate safety data from 3 company sponsored clinical studies evaluating talazoparib monotherapy at the proposed dose of 1 mg every day (QD) in patients with advanced malignancies (Phase 1 studies PRP-001 and MDV3800-14 and Phase 2 study 673-201; 164 patients total) provide the basis for the most common TEAEs. The most common TEAEs associated with talazoparib (>20%) occurring in patients who received 1 mg QD talazoparib were anemia (42.1%), fatigue (36.6%), nausea (29.3%), thrombocytopenia (25.6%), neutropenia (20.7%), and alopecia (20.1%). The most common Grade 3 or higher drug-related TEAEs occurring in ≥5% of patients were anemia (28.0%), thrombocytopenia (16.5%), and neutropenia (12.2%).

Serious adverse events (SAEs) occurred in 52 of 164 patients (31.7%) who received 1 mg QD talazoparib. Serious adverse events occurring in ≥2% of patients were pleural effusion (4.3%), anemia and dyspnea (3.7% each), and neoplasm progression and thrombocytopenia (2.4% each). Fourteen patients had SAEs considered related to talazoparib, which included

anemia (3.0%); thrombocytopenia (2.4%); platelet count decreased (1.2%); and increased transaminases, neutropenic sepsis, and vomiting (0.6% each).

A total of 12 of 164 patients (18.8%) who received 1 mg QD talazoparib had a TEAE that led to death (6 associated with the underlying malignancy including 1 also associated with bronchopneumonia; 2 dyspnea; and 1 each disease progression, lung infection, hypoxia, and respiratory failure). Of these events, none were assessed as related to talazoparib.

Among the 164 patients who received 1 mg QD talazoparib, 19.5% had a TEAE that led to dose reduction and 57.3% had a TEAE that led to dose interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

Five of 164 patients (3.0%) treated with talazoparib at a dose of 1 mg QD permanently discontinued talazoparib due to a TEAE. The TEAEs that led to study drug discontinuation were anemia, increased ALT, increased AST, metastatic breast cancer, and dyspnea.

In the ongoing Phase 3, open-label, randomized, parallel-group study (protocol no. 673-301 [EMBRACA]), talazoparib is being evaluated in patients with germline BRCA 1/2 mutations who received no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer. Patients were randomly assigned (2:1) to receive talazoparib at 1 mg/day or 1 of 4 protocol-specified, physician-choice therapies (PCT; capecitabine, eribulin, gemcitabine, or vinorelbine) determined before randomization. A total of 287 patients were included in the talazoparib arm and 144 patients in the PCT arm. The most common AEs observed with talazoparib (>20%, all grades) were anemia (52.8%), fatigue (50.3%), nausea (48.6%), neutropenia (34.6%), headache (32.5%), thrombocytopenia (26.9%), alopecia (25.2%), vomiting (24.8%), diarrhea (22%), constipation (22%), decreased appetite (21.3%), and back pain (21%). The incidence of SAEs was 31.8% in the talazoparib arm and 29.4% in the chemotherapy arm. Discontinuations due to AEs occurred in 7.7% of patients in the talazoparib arm and 9.5% of patients in the chemotherapy arm.[38] A serious TEAE of veno occlusive disease of the liver leading to death was assessed as related to talazoparib by the Investigator in a 34 year old female patient with advanced breast cancer metastatic to the axilla and bone who developed asymptomatic Grade 3 liver test abnormalities (increased ALT and AST with normal bilirubin levels) while receiving talazoparib at 0.75 mg once daily. Ten days after talazoparib dosing was discontinued due to Grade 4 thrombocytopenia, the patient had acute hepatic failure attributed to veno occlusive disease of the liver by the Investigator. However, based on the information provided, the Sponsor considered this to be an unlikely etiology, a consideration supported by 2 independent hepatologists who reviewed the case.

The combination of avelumab with talazoparib is currently being studied in Pfizer Phase 1b/2 study B9991025 (JAVELIN PARP Medley) in patients with advanced solid tumors including NSCLC, breast, ovarian, bladder, and prostate. The Phase 1b part was designed to establish the safety of talazoparib 1 mg QD in combination with avelumab 800 mg Q2W based on Cycle 1 data from 12 DLT-evaluable patients using a modified toxicity probability interval (mTPI) method. By May 18, 2018, 12 patients were enrolled in the Phase 1b portion. Overall, 3 of 12 patients (25%) experienced dose limiting toxicities during Cycle 1;

2 patients (16.7%) experienced Grade 3 thrombocytopenia, while 1 patient (8.3%) experienced a Grade 3 neutropenia.

As of 18 May 2018, the most commonly reported treatment-emergent adverse events (TEAEs) were Anemia (66.7%), Neutropenia (58.3%), and Chills and Thrombocytopenia (41.7%). Furthermore 7 patients (58%) required dose interruption of avelumab and 8 patients (66%) required dose interruption of talazoparib. The most common TEAE leading to dose interruptions of both agents was thrombocytopenia (41.7%). Notably there were no AEs leading to treatment discontinuation of any of the study drugs.

1.2.3.1. Clinical Efficacy of Talazoparib in Patients with Advanced Solid Tumors

Talazoparib, as a single-agent, has demonstrated efficacy, as well as an acceptable toxicity profile in patients with multiple types of solid tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and phosphatase and tensin homolog gene (PTEN) dysfunction, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001. In patients with advanced breast cancer, ovarian/peritoneal cancer and pancreatic cancer, ORRs of 50.0% (7 of 14), 41.7% (5 of 12) and 20% (2 of 10) were observed, respectively. More recently, talazoparib demonstrated a statistically significant improvement of PFS when compared to standard of care chemotherapy [HR = 0.54 (0.41-0.71), p<0.0001] in patients with Human Epidermal Growth Factor Receptor 2 (HER2)-negative breast cancer with germline BRCA mutation with no prior treatment in the advanced setting.[38] In the ongoing Phase 3 EMBRACA study in patients with BRCA 1/2-positive locally advanced and/or metastatic breast cancer, single-agent talazoparib demonstrated superior PFS versus physician choice chemotherapy. Median PFS was 8.6 months (95% CI: 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy [HR: 0.54 (95% CI: 0.41, 0.71), p<0.0001].[38]

1.2.3.2. Clinical Efficiacy of Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA 1/2 Mutation

Talazoparib received approval in the US as a once-daily monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline BRCA (gBRCA)-mutated, HER2-negative locally advanced or metastatic breast cancer in October 2018. Appropriate patients are selected for therapy based on an FDA-approved companion diagnostic. In April 2019, the Committee for Medicinal Products for Human Use (CHMP) of the EMA issued a positive opinion recommending marketing authorization for talazoparib in the European Union for the treatment of adult patients with germline breast cancer susceptibility gene (gBRCA)1/2-mutations, who have human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer.

1.2.3.3. PARP Inhibitor in Ovarian Cancer

The mechanism of action is validated in ovarian cancer with (United States Food and Drug Administration [US FDA]) approvals of the PARP inhibitors olaparib, niraparib, and rucaparib. Olaparib is approved for maintenance treatment for platinum-sensitive recurrent disease and BRCA mutated ovarian cancer after 3 or more lines of prior treatment.[40]

Rucaparib is approved for patients after 2 or more prior lines of treatment and BRCA-mutated disease.[41] Niraparib is approved for in the maintenance setting after platinum-based treatment for platinum sensitive recurrent disease.[42]

Olaparib was approved in EU on 16 December 2014. For niraparib, a positive Committee for Medicinal Products for Humans Use (CHMP) opinion was issued on 14 September 2017 and the European Commission decision is pending. Rucaparib is not approved in the EU.

A Phase 3 SOLO-1 study of patients with centrally confirmed germline (or somatic) BRCA1/2 mutation, showed that the use of maintenance therapy with olaparib provided a substantial benefit with regard to PFS (HR for disease progression or death = 0.30; 95% CI, 0.23 - 0.41; P<0.001).[90]

1.2.3.4. Pharmacokinetics of Talazoparib in Humans

The PK of talazoparib as a single agent following multiple daily doses was evaluated in a total of 5 studies in patients with cancer (Studies PRP-001, PRP-002, 673-201, 673-301, and MDV3800-14). Following repeated 1 mg once daily dosing to steady state, talazoparib was rapidly absorbed with a median T_{max} ranging from approximately 1.0 to 2.0 hours across studies. The talazoparib geometric mean C_{max} values ranged from 11.4 to 19.1 ng/mL and the geometric mean area under the plasma concentration-time curve for a dosing interval (AUC_{τ}) values ranged from 126 to 208 ng•hr/mL. Talazoparib C_{max} and AUC_{τ} increased dose proportionally across the dose range of 0.025 to 2 mg after administration of multiple doses. The talazoparib geometric mean steady-state C_{trough} values ranged from 2.99 to 4.95 ng/mL.

Talazoparib was eliminated slowly, with a geometric mean CL/F ranging from 4.80 to 5.53 L/hr. The mean terminal plasma $t_{½}$ of talazoparib was 89.8 hours after a single 1 mg dose of talazoparib was administered to patients with advanced solid tumors (Study MDV3800-03). After administration of multiple doses, the geometric mean CL_r was 3.34 L/hr and 3.32 L/hr in Studies PRP-001 and PRP-002, respectively, indicating that urinary excretion was a major route of elimination for talazoparib.

Following repeated oral dosing, the median talazoparib accumulation ratio (R_{ac}) ranged from 2.23 to 12.3 across the dose range of 0.025 to 2 mg (Studies PRP-001 and PRP-002). Based on the multiple dosing data from Studies PRP-001 and PRP-002 and consistent with its observed $t_{½}$ of 89.8 hours (Study MDV3800-03), talazoparib plasma concentrations reached steady state around 3 weeks after repeated daily dosing.

Study 673-103 evaluated the effect of food on the talazoparib plasma PK following administration of a single 0.5 mg dose of talazoparib oral capsule formulation in 18 healthy subjects. Food intake (a high-fat, high-calorie meal) had no impact on the AUC while reduced the C_{max} by 46%. Consistent with findings from the food effect study, population PK analysis using data from Studies 673-301, 673-201, PRP-001, and PRP-002 showed food intake decreased absorption rate but had no impact on the extent of the absorption. The reduction in the rate of absorption with food is not expected to be clinically relevant as

efficacy is generally driven by total exposure. Therefore, talazoparib can be taken without regard of food.

Based on population PK analysis, the talazoparib mean apparent volume of distribution at steady state (V_{ss}/F) was estimated to be 420 L, which is significantly greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues.

In vitro experiments with human hepatocytes and liver microsomes indicated that talazoparib undergoes minimal hepatic metabolism. Following oral administration of a single 1 mg dose of ^{14}C-talazoparib to humans, excretion of unchanged talazoparib in urine was the major route of elimination (Study MDV3800-03). No major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified in plasma. No metabolites that individually represented more than 10% of the administered dose were recovered in the urine or feces.

Talazoparib is a substrate for P-gp. Population PK analysis indicated that concomitant administration of strong P-gp inhibitors with talazoparib increased talazoparib exposure by 44.7% relative to talazoparib administered alone.

A population PK analysis for talazoparib was conducted to assess the impact of renal impairment on the CL/F using renal function as a categorical covariate defined by the baseline creatinine clearance (BCCL). The results of this analysis indicated that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (creatinine clearance [CL_{CR}], 60-89 mL/min) and moderate renal impairment (30 mL/min ≤ CL_{CR} <60 mL/min), respectively, compared to that of patients with normal renal function (CL_{CR} ≥90 mL/min). Due to limited number of severe renal impairment patients (CL_{CR} <30 mL/min), the impact of severe renal impairment on CL/F cannot be concluded. The talazoparib starting dose for patients who develop renal impairment while on study (ie, during chemotherapy period) is discussed in Section 5.6.1. The effect of renal impairment on talazoparib PK is also being investigated in the ongoing study MDV3800-01.

Results of the population PK analysis indicated that there was no effect of mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST) on talazoparib exposure. No dose adjustment is necessary for patients with mild hepatic impairment. Talazoparib has not been studied in patients with moderate (total bilirubin >1.5 to 3.0 × ULN and any AST) or severe hepatic impairment (total bilirubin >3.0 × ULN and any AST). The effect of hepatic impairment on talazoparib PK is being investigated in the ongoing study MDV3800-02.

The potential for talazoparib to affect the PK of other drugs was assessed through in vitro experiments and is described in the talazoparib IB.

1.2.4. Study Design Rationale

1.2.4.1. Rationale for Tumor Type to be Evaluated

Ovarian cancer was selected based on the following:

a. PARP inhibitors and agents targeting the PD-1/PD-L1 axis have shown clinical activity in this setting.

b. Ovarian cancer has been reported to have a high prevalence (~20%) of defects in the BRCA 1/2 genes, which have been reported to predict for sensitivity to PARP inhibitors,[43] such as talazoparib. Ovarian tumors harboring such defects have also been shown to present with increased PD-L1 expression and increased T-cell infiltration.[44,46] Increased T-cell infiltration has been associated with improved outcome in ovarian cancer,[45] and both increased T-cell infiltration and PD-L1 expression have been associated with improved response to anti-PD-1/L1 treatment.[46] Given this data, tumors harboring these defects may respond more robustly to combination treatment with talazoparib and avelumab.

c. Ovarian cancer has been reported to have a high prevalence (≥35%) of genomic scarring. Tumors with a high level of genomic scarring have been shown to have increased clinical benefit from PARP inhibitors,[48,49] and as such might also be expected to respond more robustly to the combination of talazoparib and avelumab.

Given the intrinsic links between DNA damage and immune priming outlined below, and the potential for PARP inhibition to promote DNA damage in the presence of DDR defects, ovarian cancer, with its high prevalence of such defects, represents a tumor type in which the combination of talazoparib and avelumab may optimally mediate anti-tumor activity.

1.2.4.2. Rationale for Avelumab and Talazoparib Combination

Based on the mechanisms of action discussed in Section 1.1.1 and Section 1.1.2, avelumab and talazoparib have the potential to produce additive or synergistic anti-tumor activity, with talazoparib functioning to promote immune priming and tumor immunogenicity and avelumab functioning to overcome PD-L1 mediated inhibition of any resulting anti-tumor immune response.

Specifically, the activity of avelumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells.[21] Talazoparib, via its ability to promote increased DNA damage, has the potential to promote several of these key stages of the immune response.

Firstly, talazoparib mediated cell death, via either PARP trapping or via increased DNA damage, has the potential to release antigens into the tumor microenvironment, promoting effective antigen presentation; this has been described for other therapies that lead to increased tumor cell death.[50] Secondly, DNA damage promotes inflammation via two alternative pathways, the first being activation of the NF-κB pathway via ataxia telangiectasia mutated (ATM) mediated phosphorylation of the NF-κB essential modulator

(NEMO),[8] and the second being activation of the STING pathway via generation and detection of cytosolic DNA.[9] Activation of these pathways leads to increased pro inflammatory signaling that enhances effective recognition and infiltration of tumors by immune cells, and has recently been shown to be critical to the response to checkpoint inhibition in mice.[5] Finally, DNA damage has been shown to lead to up regulation of MHC, NKG2DL, and ICOSL,[11,12] which would be expected to increase the intrinsic immunogenicity of tumor cells and enhance their recognition and killing by T-cells and NK-cells.

In keeping with these critical links between DNA damage and immune priming, talazoparib has been shown to drive the activation of STING and downstream target genes in cultured cell lines and to promote T-cell and NK-cell infiltration and activation in a mouse model of ovarian cancer.[13]

However, treatment with talazoparib has also been shown to lead to 2-3 fold increased expression of PD-L1 by tumor cells,[14] suggesting that this may represent a mechanism of resistance to possible talazoparib mediated anti-tumor immunity, and that the combination of talazoparib and anti-PD-L1 may further enhance anti-tumor activity. This hypothesis is supported by preclinical studies in syngeneic mouse models of ovarian and colorectal cancer, which demonstrate a significant improvement in overall survival in mice treated with the combination of talazoparib and an anti-mouse PD-L1, but not in mice treated with either talazoparib or anti-mouse PD-L1 alone. Studies of the PARP inhibitor olaparib in a syngeneic model of breast cancer have also shown increased tumor growth inhibition when used in combination with an anti-PD-L1 antibody.[14]

In conclusion, considering the above described mechanism of action and the preliminary clinical activity observed for the individual investigational products and agents of the same class (see Section 1.1.1, Section 1.1.2, and Section 1.2), the avelumab and talazoparib combination is proposed for evaluation in patients with advanced epithelial ovarian cancer.

1.2.4.3. Rationale for Avelumab in Combination with Chemotherapy

There are emerging data supporting the rationale for combinations of immune checkpoint inhibitors with chemotherapy.[16,18] Chemotherapy has been shown to have immunostimulatory properties by stimulating the release of neoantigens and adjuvants from dying cells, increasing susceptibility to immune attack, and preferentially reducing immunosuppressive cells such as T regulatory cells.[19-22] Certain chemotherapy agents, including platinum-based agents, are mutagenic.[23] 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, 5-fluorouracil) showed improved anti-tumor activity over single agent chemotherapy.[1]

Clinical proof of concept for concurrent administration of chemotherapy and checkpoint inhibition, followed by single agent checkpoint inhibition maintenance therapy, was provided in the randomized Phase 2 trial ‘Keynote -21’ in which (anti-PD-1 agent) pembrolizumab was combined with platinum-based chemotherapy in (non-squamous) NSCLC.[24] Both ORR

and PFS were statistically significantly and clinically relevantly increased (ORR 59% vs 29% and median PFS 13 months versus 8.9 months (Hazard Ratio 0.53 [95% CI: 0.31, 0.91; p=0.01]). Recently, the results were updated[25] and the HR for OS was 0.59, which did not reach statistical significance. Phase 3 trials with pembrolizumab, nivolumab, and atezolizumab in combination with chemotherapy are ongoing or recently released preliminary results in NSCLC and various other solid tumors. A recent press release from Merck Serono in January 2018 indicated that pembrolizumab in combination with chemotherapy for first line treatment of patients with metastatic NSCLC did in fact meet its dual primary endpoint of OS and PFS based on an interim analysis conducted by the independent Data Monitoring Committee and resulted in significantly longer OS and PFS than pemetrexed plus platinum chemotherapy alone. The safety profile of pembrolizumab in this combination was consistent with that previously observed. Additionally, preliminary results of the phase 3 IMpower 150 trial were presented at the European Society for Medical Oncology (ESMO) IO 2017 congress. The PFS survival comparison indicated the combination of atezolizumab, bevacizumab and chemotherapy was superior to bevacizumab and chemotherapy alone with a median PFS of 8.3 versus 6.8 months (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.52, 0.74; P <0.0001) in the intention-to-treat (ITT) wild type (WT) population.[51] No new safety signals were observed with combination therapy.

Avelumab is being tested concurrently and sequentially with chemotherapy in frontline ovarian cancer (B9991010 with carboplatin and paclitaxel) and as a single agent or concurrently with chemotherapy in the platinum-resistant and platinum-refractory population (B9991009 with PLD). In addition, avelumab is also being evaluated with chemotherapy and radiotherapy in B9991016, in locally advanced head and neck cancer, with azacitidine and bendamustine in two arms of B9991011 in diffuse large B-cell lymphoma (DLBCL) and with cisplatinum and pemetrexed in NSCLC and cisplatinum and gemcitabine in UC in B9991023. Lastly, sequential/ maintenance treatment is tested in B9991001 in UC. The clinical proof of concept for sequential treatment came from the PACIFIC trial.[25] In this placebo controlled randomized Phase 3 trial, 713 stage III patients with NSCLC were treated with either anti-PD-L1 agent durvalumab or placebo after radiotherapy-chemotherapy (2:1 ratio). The study met its co-primary end point of progression free survival with a large treatment effect: HR 0.52 (95% CI: 0.42-0.65). The median PFS for durvalumab (16.8 [95% CI: 13.0 - 18.1] months) was almost triple that of placebo (5.6 [95% CI: 4.6 – 7.8] months). However, the optimal sequence of chemotherapy and immunotherapy (concurrent vs sequential) remains to be determined, and a strong rationale exists both for concurrent and sequential administration.

In summary, avelumab has the potential to improve the durability of response to platinum-based therapy in the frontline maintenance setting.

1.2.5. Rationale for the Investigational Product Doses

1.2.5.1. Avelumab

To date, avelumab has been administered at the clinically active, safe, and tolerable dose of 10 mg/kg Q2W to more than 1700 patients across multiple indications. Furthermore, this 10 mg/kg Q2W avelumab dosing regimen has been approved by the US FDA for MCC and UC, as well as for MCC in the European Medicines Agency (EMA), Switzerland, Japan, Australia, and Israel. Avelumab was originally dosed on a mg/kg basis in order to reduce inter subject variability in drug exposure. However, emerging data for mAbs, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body weight independent) dosing regimens.[52,53,54] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired data across 3 single agent avelumab studies in 1827 patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are less variable with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the population median weight. Low weight subjects tended towards marginally lower exposures relative to the rest of the population when weight based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, based on these simulations, the 800 mg Q2W dosing regimen is expected to result in C_{trough} >1 μg/mL required to maintain avelumab serum concentrations at >95% TO throughout the entire Q2W dosing interval in all weight categories.

Therefore, in this clinical trial, a fixed dosing regimen of 800 mg administered as a 1-hour IV infusion Q2W will be utilized for avelumab during the maintenance period.

Furthermore, in Arm A, avelumab will be dosed every 3 weeks during the chemotherapy period in order to align with the dosing of chemotherapy, which will also be every three weeks. In an effort to mitigate unexpected hematologic toxicity and considering that the tolerability of avelumab in patients with severe myelosuppression is currently not well characterized, a Q3W schedule was adopted for avelumab in this study in order to avoid dosing of avelumab during the expected hematologic nadir period for the selected chemotherapy regimens. In order to align with the dosing of chemotherapy and to avoid dosing at the nadir, PK and PD data support the exploration of Q3W dosing posology. The preliminary data from clinical studies suggest >90% TO is required for clinical benefit. PK simulations show that, the 800 mg Q3W dosing regimen is expected to provide median plasma C_{trough} greater than 1 μg/mL at 21 days, yielding a mean TO >90% over the entire Q3W dosing interval (Pfizer, data on file), including when used in combination with chemotherapy or other anti-cancer immunotherapies.

1.2.5.2. Talazoparib

The dose level of talazoparib to be evaluated in this study is supported by clinical studies in patients with advanced malignancies and breast cancer. In a Phase 1 study PRP-001, patients with advanced or recurrent solid tumors were treated with escalating doses of talazoparib from 0.025 to 1.1 mg QD. Data from 1 mg QD dose in that study demonstrated objective responses or clinical benefit (CR, PR, or stable disease ≥24 weeks) in patients with breast, ovarian/peritoneal, pancreatic cancer, small cell lung cancer (SCLC), and Ewing sarcoma. For the 17 patients with ovarian cancer treated at talazoparib doses <1 mg QD, 7 patients (3 at 0.9 mg, 2 at 0.6 mg and 1 each at 0.2 and 0.1 mg) had objective responses resulting in an overall response rate of 41.2%. All patients with a response had a best overall response of PR except for 1 patient treated at 0.9 mg QD who had a best overall response of CR. In addition, sustained pharmacodynamic inhibition of PARP activity measured in PBMNCs was observed at dose levels ≥0.6 mg QD.

Furthermore, in the Phase 3 study 673-301 (EMBRACA), 286 patients with locally advanced or metastatic breast cancer were treated with the single-agent maximum tolerated dose of talazoparib at 1 mg QD established in the dose escalation phase of study PRP-001. In EMBRACA, the median treatment duration was 6.1 months; however, 52% of the patients required at least 1 dose reduction and 28% required >1 dose reduction. Anemia (38.1%), neutropenia (19.2%) and thrombocytopenia (10.5%) were the most common TEAEs leading to dose modifications in this study.

The safety of avelumab in combination with talazoparib is currently being evaluated in Study B9991025, a Phase 1b/2 study in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors. The Phase 1b part was completed on 18 May 2018 and the recommended Phase 2 dose for talazoparib administered orally in combination with avelumab 800 mg IV Q2W was 1 mg QD. Preliminary evaluation of safety data from patients receiving the 1 mg QD talazoparib dose in combination with avelumab showed that 8 patients (66.7%) experienced AEs that led to talazoparib dose interruption. The 3 DLT's observed, consisting of thrombocytopenia (n=2) and neutropenia (n=1), represent early hematopoietic toxicity. Anemia has emerged as the most common TEAE (66.7%) and 25% of these patients required transfusions.

As the duration of maintenance treatment in this study with talazoparib both in combination with avelumab (Arm A) and as a single-agent (Arm B) will be for up to 24 months, administration of a talazoparib dose that provides improved long-term tolerability, including a reduced frequency of TEAE leading to dose interruption and reduction is desired. Exposure-response analysis of data from talazoparib clinical studies showed that higher talazoparib exposure is associated with longer progression-free-survival (PFS) and also with a higher risk for Grade 3 or higher anemia and thrombocytopenia. Therefore, dose reduction is an effective way to lower the probability of experiencing the AEs. Given that objective responses were observed in study PRP-001 at talazoparib doses of ≥0.1 mg QD and that pharmacodynamic inhibition of PARP activity was similar at dose levels ≥0.6 mg QD, the B9991030 study will use a starting dose of 0.75 mg QD for talazoparib both Arms A and B for improved long-term tolerability while maintaining adequate PARP inhibition. The

starting dose of talazoparib for patients with moderate renal impairment (CL_{CR}=30-59 mL/min) will be 0.5 mg QD to account for the lower talazoparib clearance. Patients who already started at 1 mg QD talazoparib prior to Protocol amendment 1 must be informed and dose reduce to 0.75 mg QD at their subsequent study visit after protocol IRB/EC approval.

1.2.6. Rationale for Randomization Stratification

The combination of avelumab and talazoparib is predicated on the ability of talazoparib to promote DNA damage, which leads to increased inflammation, immune priming and tumor immunogenicity, and on the ability of avelumab to overcome PD-L1 mediated inhibition of any anti-tumor immune response resulting from this priming event. Based on this mechanism of action, the combination of avelumab and talazoparib is expected to be differentially effective in patients that have greater sensitivity to talazoparib-mediated DNA damage.

Clinical studies have indicated that the greatest sensitivity to PARP inhibitors, such as talazoparib, is observed in tumors that have defects in the BRCA1 or BRCA2 genes.[43] Such defects result in defective repair of double strand DNA breaks, such breaks accumulate following PARP inhibition, leading to cell death.

Given the potential for differential activity of talazoparib and avelumab as monotherapy, and in combination, in patients with and without defects in BRCA1 or 2, the randomization of patients in this study will be stratified by BRCA 1/2 status.

BRCA1/2 status at the time of randomization for patients will be determined based on pre-existing results obtained from a blood or saliva based test. Where no such historic test result exists, a de novo blood test will be conducted during the screening period in order to establish BRCA1/2 status. Patients will be defined as germline (g)BRCA positive (+) if they are shown to carry an expected or known pathogenic mutation in either the BRCA1 or BRCA2 genes. All other patients will be defined as gBRCA negative (-).

The high-risk target population of B9991030 includes patients who are candidates for neoadjuvant chemotherapy followed by IDS and patients who receive adjuvant chemotherapy following incomplete primary debulking surgery. A number of recent Phase 3 studies have successfully combined adjuvant and neoadjuvant patient populations (GOG-262, ICON 8, B9991010). In addition, recent studies in women with Stage III and IV ovarian cancer comparing neoadjuvant chemotherapy to primary debulking surgery have demonstrated that survival with upfront chemotherapy is non-inferior to primary surgery (EORTC55971 and CHORUS). However, considering the overall difference in the treatment regimen, the randomization of patients in this study will also be stratified by the chemotherapy approach: adjuvant vs. neoadjuvant.

The extent of residual disease is an important prognostic factor for patients undergoing primary debulking surgery (PDS) followed by adjuvant chemotherapy. The Gynaecologic Oncology Group (GOG) currently defines “optimal” outcome of cytoreductive surgery as having residual disease of 1 cm or less, with complete cytoreduction being the ideal surgical

outcome. However, women with residual disease ≤1 cm (optimal surgical outcome) showed improved PFS and OS compared to women with suboptimal surgical outcome or residual disease >1 cm (Chan 2003; Winter 2008).[55] Based on these data, randomization will also be stratified by resection status (residual disease >1 mm and ≤1 cm vs residual disease >1 cm) in this study.

1.2.7. Rationale for Biomarker Assessments

As mentioned above the combination of avelumab and talazoparib is expected to be differentially effective in patients that have greater sensitivity to talazoparib-mediated DNA damage. While defects in BRCA1/2 represent one potential marker of such sensitivity, it is clear, from studies of both niraparib[48] and rucaparib[49] that patients whose tumors lack BRCA1/2 defects can also be sensitive to PARP inhibition. In particular, those whose tumors showed markers of genomic scarring, such as loss of heterozygosity (LOH), which are suggestive of ongoing or historic DNA damage, show increased sensitivity. These data indicate that PARP inhibitor activity is not limited to tumors deficient in BRCA but is also seen in tumors with other defects in DDR, sometimes referred to as being homologous recombination deficient or having a BRCAness phenotype.[43] Tumors with defects in DDR genes have also been shown to present with a more inflamed tumor phenotype in a number of settings,[55,44,59] and therefore, are also expected to respond better to avelumab treatment.

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To enable the above mentioned biomarker assessments, the provision of pre-treatment tumor specimens from an archive tumor tissue sample or *de novo* biopsy is mandatory for patients randomized to the study.

Given the limited ability to assess tumor tissue based biomarkers longitudinally, a number of biomarkers will also be measured in peripheral blood at a number of time point's pre-treatment and post-treatment. The primary aim of these measurements is to identify pharmacodynamic or mechanistic biomarkers for the combination of avelumab and talazoparib. Such biomarkers may have value in predicting response or resistance to treatment. Planned assessments include, but are not limited to, gene expression profiling, diversity of TCR sequences by DNA sequencing, and levels of circulating soluble factors such as cytokines and chemokines.

Optional *de novo* biopsy tissue is also requested, where not clinically contraindicated, at the End of Treatment visit or in the event of permanent treatment discontinuation due to disease progression, in order to support an understanding of emerging resistance mechanisms.

Finally, circulating tumor (ct)DNA will be collected at baseline, once during induction chemotherapy, following induction prior to initiation of maintenance treatment, once during maintenance treatment and at End of Treatment in order to enable assessment of genomic biomarkers that may predict for response or drive resistance, CCI [redacted].

CCI [redacted]

CCI [redacted]

1.3. Summary of Benefit/Risk Assessment

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

The benefit risk relationship has been carefully considered in the planning of this trial. Avelumab demonstrated clinical activity in patients with advanced solid tumors, including NSCLC (first line and second line or higher), breast cancer, CRPC, UC and ovarian cancer in the expansion cohorts of the ongoing Phase 1 Study EMR 100070- 001, as described in Section 1.2.2. The clinical safety data available to date with single agent avelumab in patients with advanced solid tumors suggest an acceptable safety profile, as described in Section 1.2.2.1. Most of the observed adverse events were either in line with those expected in patients with advanced solid tumors or with similar class effects of mAbs blocking the PD-1/PD-L1 axis. Infusion-related reactions, including hypersensitivity and 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 measures include guidelines for treatment interruption and discontinuation in case of irAEs, as well as mandatory pre-treatment with an antihistamine and acetaminophen prior to the first 4 infusions of avelumab and as clinically indicated thereafter.

Talazoparib also has demonstrated single agent clinical activity in patients with advanced solid tumors with DNA repair pathway abnormalities, particularly those associated with BRCA and PTEN dysfunction, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001, as described in Section 1.2.3. The clinical safety profile of talazoparib supports its use as both a single agent and in combination with cancer therapies. The most common TEAEs associated with single agent talazoparib administration (>20%) were myelosuppression (eg, anemia, thrombocytopenia, neutropenia), gastrointestinal toxicity (eg, nausea, diarrhea, vomiting), and fatigue with severe and serious adverse events mostly associated with myelosuppression. These adverse events were primarily Grade 1 or 2 severities and typically resolved with temporary dose interruptions or reductions.

Based on the manageable safety profiles of avelumab and talazoparib administered as single agents, the lack of anticipated severe overlapping severe toxicities, and the anticipated enhanced anti-tumor activity, the projected benefit-risk relationship of avelumab given in combination with talazoparib is expected to be favorable for investigation in this population of patients with advanced ovarian cancer.

2. STUDY OBJECTIVES AND ENDPOINTS (OBSOLETE)

The original study objectives and endpoints are no longer applicable and/or feasible.

The purpose of protocol amendment 2 is to reduce study-specific procedure assessments (ie, remove efficacy, physical examination, electrocardiogram, ePROs, tumor assessments, PK and Biomarkers) for the ongoing patients.

The schedule of activities (SOA) found in Appendix 6 is replacing the previous SOA and has been revised to decrease the frequency of study procedures while maintaining appropriate assessment of patient safety. The new SOA is effective with IRB/EC approval of amendment 2.

Primary Objective:	**Primary Endpoint:**
• To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging PFS in patients with advanced ovarian cancer with defects in DNA damage repair (DDR+).	• PFS as determined based on BICR assessment per RECIST v1.1 in patients with newly diagnosed advanced ovarian cancer with defects in DNA damage repair (DDR+).
Secondary Objectives:	**Secondary Endpoints:**
• To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging overall survival (OS) in patients with advanced ovarian cancer with defects in DNA damage repair (DDR+). • To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging PFS in patients with advanced ovarian cancer unselected for DDR status. • To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in prolonging OS in patients with advanced ovarian cancer unselected for DDR status. • To evaluate the effect on PFS and OS of platinum-based chemotherapy followed by talazoparib maintenance versus platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance in patients with advanced ovarian cancer with DDR+ and unselected for DDR status. • 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 avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance in Arm A as well as well as PK of talazoparib in combination with avelumab (Arm A) and as a single agent (Arm B). • To evaluate the immunogenicity of avelumab in	• OS in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS based on BICR assessment per RECIST v1.1 in patients unselected for DDR status. • PFS based on investigator assessment per RECIST v1.1 in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS2 based on investigator assessment in patients with tumors that are DDR+ and in patients unselected for DDR status. • PFS based on investigator assessment per Gynecological Cancer Intergroup (GCIG) criteria in patients with tumors that are DDR+ and in patients unselected for DDR status. • AEs (as graded by NCI CTCAE v4.03); laboratory abnormalities (as graded by NCI CTCAE v4.03); vital signs (blood pressure, pulse rate); electrocardiograms (ECGs). • PK parameters, including C_{trough} and C_{max} for avelumab and C_{trough} for talazoparib. • Anti-drug antibodies (ADA) and neutralizing antibody (NAb) against avelumab. • Disease related symptoms and treatment side effects as measured by the NCCN-FACT FOSI-18 and health-related quality of life (HRQOL) as measured by NCCN-FACT FOSI-18 and the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L). • PD-L1 expression, TMB, genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue. • Assessment of defects in a panel of key oncogenes, including several considered critical to effective DDR and TMB in ctDNA at baseline.

Arm A (avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance). • To evaluate the effect of avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance and platinum-based chemotherapy followed by talazoparib maintenance versus platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance on patient reported outcome (PRO) including the assessments of disease-related symptoms, treatment side effects and health-related quality of life (HRQoL). • To assess the correlation of anti-tumor activity with PD-L1 expression, tumor mutational burden (TMB) and with potential biomarkers of PARP inhibitor sensitivity in baseline tumor tissue. • To assess the correlation of anti-tumor activity with TMB and potential biomarkers of PARP inhibitor sensitivity in baseline circulating tumor (ct) DNA.	
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

This is a Phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of avelumab in combination with chemotherapy followed by maintenance therapy of avelumab in combination with the PARP inhibitor talazoparib in patients with previously untreated advanced ovarian cancer. Patients must meet full eligibility criteria as specified in Section 4.

The study design, including the number of patients to be randomized in each treatment arm, is illustrated in Figure 1.

3.1. Study Overview

Approximately 720 patients (including a minimum of 360 patients with tumors that are DDR+) who are candidates for frontline chemotherapy followed by maintenance were planned to be randomized in a 2.5:1:2.5 ratio stratified by germline BRCA 1/2 mutational status (gBRCA+ vs gBRCA-) and resection status (adjuvant with >1 mm and ≤1 cm residual disease vs adjuvant with >1 cm residual disease vs neoadjuvant) to one of the following treatment arms:

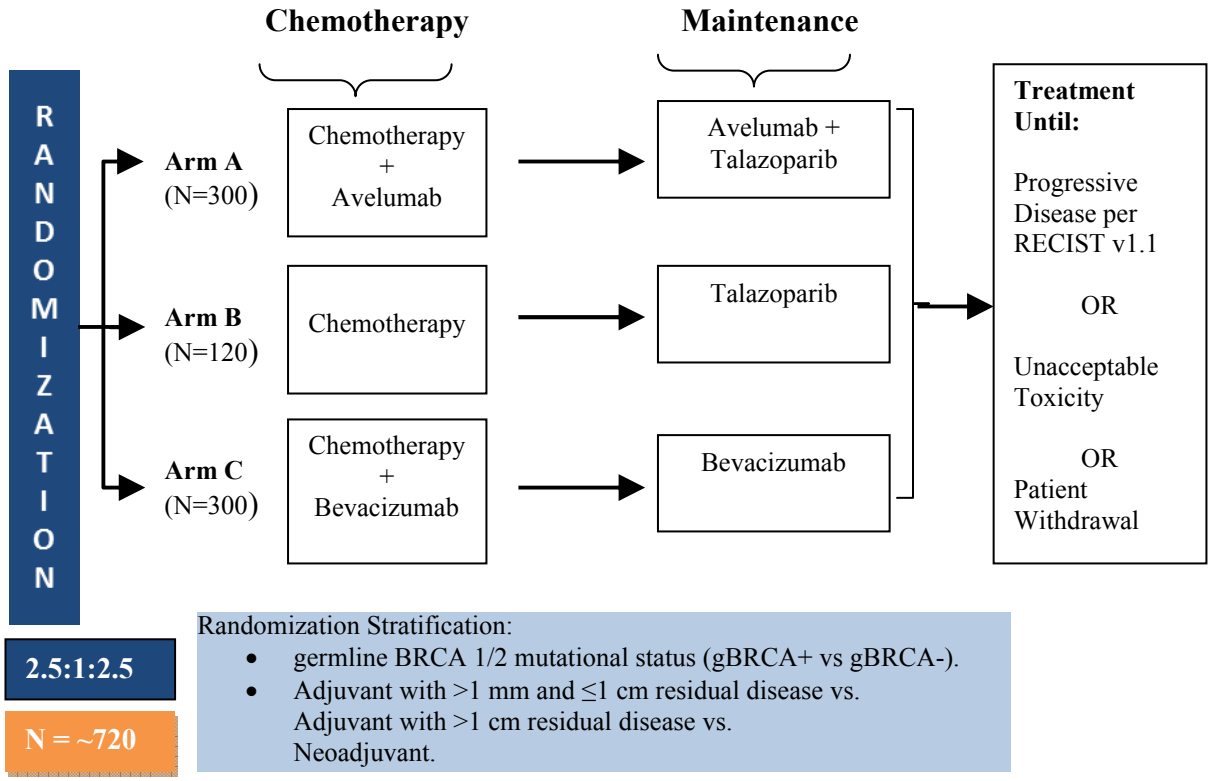
- Arm A: platinum-based chemotherapy + avelumab followed by avelumab + talazoparib maintenance;
- Arm B: platinum-based chemotherapy followed by talazoparib maintenance;
- Arm C: platinum-based chemotherapy + bevacizumab followed by bevacizumab maintenance.

As of 19 March 2019, no new patients could be screened or randomized.

Intravenous carboplatin and paclitaxel will be used as the chemotherapy backbone, consisting of Q3W carboplatin and paclitaxel.

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 to be followed, upon recovery from surgery, by the remaining 3 cycles of chemotherapy.

Figure 1. Study Schematic



gBRCA = germline BReast CAncer gene; N = number of patients

3.1.1. Study Treatment Plan

The study period includes two treatment periods, the chemotherapy period and the maintenance period. For the purpose of scheduling evaluations, providing clarity on assessments, and consistent on-treatment assessments across all three treatment arms, the definition of cycle length varies between the chemotherapy period and the maintenance period. In the chemotherapy period, a cycle is defined as 3 weeks (21 days), and due to the biweekly schedule of avelumab and the Q3W schedule for bevacizumab, a cycle in the maintenance period is defined as 6 weeks (42 days). See Section 1.2.5.1 for additional information.

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

Arm A:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.
- Avelumab 800 mg administered intravenously on Day 1 of each 3-week cycle for 6 cycles.

Arm B:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.

Arm C:

- Paclitaxel 175mg/m^2 IV over 3 hours followed by Carboplatin AUC 5or 6 IV over 15-60 minutes on Day 1 of each 3-week cycle for 6 cycles.

- Bevacizumab 15mg/kg IV on Day 1 of each 3-week cycle beginning with Cycle 2 for adjuvant patients (may begin with cycle 1 if surgery completed >4 weeks prior to randomization and no contraindications), and for neoadjuvant patients, bevacizumab will be given on Day 1 of each 3-week cycle for Cycles 1, 2, 5, and 6.

For patients who are enrolled to undergo neoadjuvant chemotherapy with interval debulking surgery, the first 3 cycles of chemotherapy will be administered prior to interval debulking surgery. Patients will stay on study regardless of the surgery outcome (eg, extend of residual disease) and will receive the remaining 3 cycles of chemotherapy.

Patients who have to discontinue both chemotherapy agents (carboplatin and paclitaxel) for unacceptable toxicities prior to the end of Cycle 6 may enter maintenance period, if deemed clinically acceptable by the investigator and will receive avelumab and talazoparib (Arm A) or talazoparib (Arm B), or bevacizumab (Arm C).

Maintenance period should begin within 4 weeks of the last dose of chemotherapy. The first visit of maintenance therapy will be designated maintenance Cycle 1 Day 1 even if the last chemotherapy cycle was not completed.

For the **maintenance period** of the study, study drugs will be assigned and given as follows.

Arm A:

- Avelumab 800 mg administered intravenously on Days 1, 15, and 29 of each 6-week cycle in combination with talazoparib 0.75 mg self-administered orally once per day.

Arm B:

- Talazoparib 0.75 mg self-administered orally once a day, every day of each 6-week cycle.

Arm C:

- Bevacizumab 15 mg/kg administered intravenously on Days 1 and 22 of each 6-week cycle.

Effective with IRB/EC approval of amendment 2, patients will receive study treatment until progressive disease (PD) as assessed by the investigator, unacceptable toxicity, or withdrawal of consent, whichever is earliest. For avelumab and talazoparib, the maximum duration of maintenance treatment is 24 months. For bevacizumab, the maximum duration of treatment is 21 or 22 doses, per local approval, including the period of initial chemotherapy.

Patients who discontinue all study treatment and have PD based on investigator assessment will be followed for a 90-day Safety Follow-up Period.

3.1.1.1. 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 A or with bevacizumab in Arm C), then treatment will be held, and interval debulking surgery will be performed. According to institutional practice, upon recovery from surgery, the remainder of chemotherapy (with avelumab in Arm A and with bevacizumab in Arm C) should be administered for a maximum of 6 cycles of chemotherapy. See Sections 5 and 5.10.2.1 for further details.

3.2. Safety Monitoring

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

An external data monitoring committee (E-DMC) was planned to have an initial review of safety data, without an enrollment hold, after approximately 30 patients in the study (approximately 12 patients in the avelumab plus talazoparib combination, Arm A) have been treated and followed for at least 4 weeks after the first dose in the maintenance period.

As of 19 March 2019, the initial E-DMC meeting had not yet occurred. This study will no longer use an E-DMC.

4. PATIENT ELIGIBILITY CRITERIA

Enrollment was stopped, and patients can no longer be screened as of 19 March 2019.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

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

4.1. Inclusion Criteria

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 American Joint Committee on Cancer (AJCC)/UICC TNM and International Federation of Gynecology and Obstetrics (FIGO) Staging System 2014 edition), including carcinosarcoma with high-grade serous component.

2. Patients must be candidates for bevacizumab in combination with platinum based chemotherapy and previously untreated.

3. Must have completed a primary surgical debulking procedure, or be candidates for neoadjuvant chemotherapy with planned interval debulking surgery.

    a. Patients who completed primary debulking must have had incompletely resected disease that is macroscopically/grossly visible and at least with lesions >1 mm per operative records and be randomized at a maximum of 8 weeks after surgery.

    b. For patients who are candidates for neoadjuvant chemotherapy, the diagnoses must have been confirmed by:

        - Core tissue (not fine-needle aspiration) biopsy is required for diagnosis. The tissue must be consistent with inclusion criteria #1 above.

        - 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, then workup should be negative for the presence of a primary gastrointestinal or breast malignancy (<6 weeks before start of neoadjuvant treatment).

        - 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 25 slides, together with an accompanying original Hemotoxylin and Eosin (H&E) slide. 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.

    - Sites may randomize/enroll patients who meet all other eligibility criteria while awaiting central confirmation of tissue acceptance, but must provide additional tumor samples in the event that the central lab review shows insufficient sample quality.

5. Eastern Cooperative Group (ECOG) performance status 0-1 (see Appendix 2).

6. Age ≥18 years (or ≥20 years in Japan).

7. Adequate bone marrow function including: absolute neutrophil count (ANC) ≥1,500/mm^3 or 1.5 x 10^9/L; Platelets ≥100,000/mm^3 or ≥100 x 10^9/L; hemoglobin ≥9.0 g/dL (may have been transfused).

8. Adequate hepatic function defined by a total bilirubin level ≤1.5 x upper limit of normal range (ULN), an ALT/AST level ≤2.5 x ULN.

9. Adequate renal function by estimated creatinine clearance ≥60 mL/min as calculated using the Cockcroft-Gault method or by 24 hour urine collection for creatinine clearance or according to local institutional standard method.

10. Adequate blood coagulation parameters: International normalized ratio (INR) ≤1.5 and aPTT <1.2 times the upper limit of normal.

11. Ability to swallow oral study drugs.

12. 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.

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

14. Patients of childbearing potential and at risk for pregnancy must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency) as outlined in this protocol for the duration of the study and for at least 30 days after the last dose of avelumab, 7 months after the last talazoparib dose, and for 6 months after the last dose of bevacizumab. Patients of non-childbearing potential must meet at least 1 of the following criteria:

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as 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) or mucinous tumors.

2. Patients for whom intraperitoneal cytotoxic chemotherapy is planned.

3. Prior exposure to immunotherapy with interleukin (IL)-2, interferon alpha (IFN-α), an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen 4 (anti-CTLA4) antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, excluding therapeutic anticancer vaccines.

4. Prior treatment with a PARP inhibitor.

5. Prior treatment with any anti-vascular endothelial growth factor (VEGF) drug, including bevacizumab.

6. Major surgery (other than debulking or exploratory surgery for ovarian cancer) for any reason within 4 weeks prior to randomization and/or incomplete recovery from surgery.

7. Prior radiotherapy to any portion of the abdominal cavity or pelvis. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

8. Prior targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their ovarian, peritoneal primary or fallopian tube carcinoma.

9. Prior organ transplantation including allogenic stem cell transplantation.

10. Diagnosis of Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).

11. Known symptomatic brain metastases requiring steroids. Patients with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study enrollment, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and are neurologically stable.

12. Current or anticipated use within 7 days prior to the first dose of talazoparib or anticipated use during the study of a P-glycoprotein (P-gp) inhibitor, P-gp inducer, or breast cancer resistance protein (BCRP) inhibitor (See Section 5.10.6 for specific list of medications).

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

14. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroidism not requiring immunosuppressive treatment are eligible.

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

16. Uncontrolled hypertension, defined as systolic >140 mm Hg or diastolic >90 mm Hg documented by 2 blood pressure readings taken at least 1 hour apart. Use of antihypertensive medications to control blood pressure (BP) is allowed.

17. Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.

18. Active infection requiring systemic therapy.

19. Known history of testing positive for human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS).

20. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test is positive).

21. Administration of a live vaccine within 30 days prior to study enrollment.

22. Known severe hypersensitivity reactions to investigational products or any component in their formulations or to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥3).

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

24. 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) and *in situ* carcinoma of the bladder.

25. 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, including their family members, directly involved in the conduct of the study.

26. Participation in other clinical studies involving investigational drug(s) within 4 weeks prior to study randomization and/or during study participation.

27. Known history of immune colitis, inflammatory bowel disease, immune pneumonitis, or pulmonary fibrosis.

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

29. Pregnant patients or breastfeeding patients.

4.3. Lifestyle Requirements

In this study, patients will receive avelumab for which the teratogenic risk is currently unknown in combination with talazoparib, which has been associated with teratogenic risk. All fertile female patients who are of childbearing potential, who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency as defined below) throughout the study and continue for at least 30 days after the last dose of avelumab, 7 months after the last dose of talazoparib, and for 6 months after the last dose of bevacizumab. The Investigator or his or her designee, in consultation with the patient, will confirm that 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 that the patient has been instructed in their consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the patient of the need to use 2 methods of contraception at least one of which is considered to be highly effective with low user dependency as defined below) consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart. In addition, the investigator or designee will instruct the patient to call immediately if 1 or both of the selected contraception methods is 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 hormonal methods of contraception associated with inhibition of ovulation (eg, inserted, injected, implanted), 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 separate spermicide product (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 or 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, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

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

For this study, the investigational products are avelumab and talazoparib. Bevacizumab will be considered investigational product only in countries where a treatment used in the standard therapy arm to be deemed an investigational product is required by law.

The study includes two treatment periods, the chemotherapy period and the maintenance period.

For the **chemotherapy period** of the study, study drugs will be given as follows:

Arm A:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.

- Avelumab 800 mg administered intravenously on Day 1 of each 3-week cycle for 6 cycles.

On dosing days when both chemotherapy and avelumab are infused (Day 1), avelumab will be infused after chemotherapy.

Premedication for chemotherapy is described in Section 5.4.1.1 and premedication for avelumab is described in Section 5.5.1.2.

Arm B:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Days 1 of each 3-week cycle for 6 cycles.

Arm C:

- Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 5 or 6 IV over 15-60 minutes on Day 1 of each 3-week cycle for 6 cycles.

- Bevacizumab 15 mg/kg IV Day 1 of each 3-week cycle beginning with Cycle 2 for adjuvant patients, and for neoadjuvant patients, bevacizumab will be given on Day 1 of each 3-week cycle for Cycles 1, 2, 5, and 6.

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.

Patients who have to discontinue both chemotherapy agents (carboplatin and paclitaxel) for unacceptable toxicities prior to the end of Cycle 6 may enter maintenance period, if deemed clinically acceptable by the investigator and will receive avelumab and talazoparib (Arm A) or talazoparib (Arm B), or bevacizumab (Arm C).

Maintenance period should begin within 4 weeks of the last dose of chemotherapy. The first visit of maintenance therapy will be designated maintenance Cycle 1 Day 1 even if the last chemotherapy cycle was not completed.

For the **maintenance period** of the study, study drugs will be given as follows.

Arm A:

- Avelumab 800 mg administered intravenously on Days 1, 15 and 29 of each 6-week cycle in combination with talazoparib 0.75 mg self-administered orally once per day.

On dosing days when both investigational products are administered, talazoparib will be administered first.

Arm B:

- Talazoparib 0.75 mg self-administered orally once a day, every day of each 6-week cycle.

Arm C:

- Bevacizumab 15 mg/kg administered intravenously on Days 1 and 22 of each 6-week cycle.

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

Enrollment was stopped, and patients can no longer be allocated to treatment as of 19 March 2019.

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.

Allocation of patients will be stratified according to germline BRCA 1/2 mutational status (gBRCA+ vs gBRCA-) and resection status (adjuvant with >1 mm and ≤1 cm residual disease vs adjuvant with >1 cm residual disease 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, and the patient number. 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.

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 2.5:1:2.5 ratio as follows:

	Chemotherapy Period	Maintenance Period
Arm A	Chemotherapy + Avelumab	Avelumab + Talazoparib
Arm B	Chemotherapy	Talazoparib
Arm C	Chemotherapy + Bevacizumab	Bevacizumab

5.2. Patient Compliance

The information related to each trial drug administration (ie, infusions), including the date, time (except for talazoparib), and dose of study drug, will be recorded in the CRF. The Investigator will make sure that the information entered into the CRF regarding drug administration is accurate for each patient. Any reason for noncompliance should be documented.

5.2.1. Patient Compliance with Avelumab

All doses of avelumab will be administered at the investigational site by well-trained medical staff. The start and stop times of the avelumab infusion, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of avelumab infusion will also need to be recorded in the patients' medical records. The vials of avelumab that are assigned and prepared for patients will be recorded in the pharmacy records. These records will all be available for Sponsor representatives to verify compliance.

The site will complete the required dosage Preparation Record located in the Investigational Product manual (IP manual) for avelumab. The use of the supplied Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation of the avelumab dose. This may be used in place of the Preparation Record after approval from the Sponsor and/or designee.

Non-compliance is defined as a patient missing >1 infusion of avelumab for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 6 weeks for non-medical reasons, then the patient would also be considered noncompliant.

5.2.2. Patient Compliance with Talazoparib

Patients will be required to return all unused talazoparib capsules every cycle. The number of capsules returned by the patient should be counted, documented, and recorded by site personnel in the patient's medical record and reconciled with the patient's dosing diary to support the talazoparib accountability process. Study site personnel must make reasonable efforts to obtain study drug packaging and any unused capsules from patients who do not routinely return them at study site visits. Unreturned capsules will be considered to have been taken unless reported otherwise by the patient.

Additionally, a patient dosing diary and dosing card will be provided to aid in patient compliance with the dosing instructions. The diary will be completed by the patient to include taken, missed or changed talazoparib doses. The total dose of talazoparib taken each day will be recorded in the dosing diary. On days when the patient's talazoparib dose is given at the clinic due to combination dosing with avelumab and/or scheduled PK sample collection, the time of talazoparib dose administration and the total dose of talazoparib taken will be recorded in the patient's dosing records that are included in the medical chart.

Treatment compliance (reported as a percent) will be defined as the number of capsules taken during the study divided by the expected number of capsules, multiplied by 100.

5.2.3. Patient Compliance with Bevacizumab

All doses of bevacizumab will be administered at the investigational site by well-trained medical staff. The start and stop times of the infusion, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of infusion will also need to be recorded in the patients' medical records. The vials of bevacizumab that are assigned and prepared for patients will be recorded in the pharmacy records. These records will all be available for Sponsor representatives to verify compliance.

The site will complete the required dosage Preparation Record located in the Investigational Product manual (IP manual) for bevacizumab. The use of the supplied Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation of the bevacizumab dose. This may be used in place of the Preparation Record after approval from the Sponsor and/or designee.

Noncompliance is defined as a patient missing >1 infusion of bevacizumab for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 6 weeks for non-medical reasons, then the patient would also be considered noncompliant.

5.3. Investigational Product Supplies

Clinical Trial supplies will be shipped to the study sites by Pfizer Global Clinical Supply (GCS), Worldwide Research and Development (WRD), and will include 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. Dosage Form(s) and Packaging

Packaging and labeling for all study drugs will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Guidelines (GMP) guidelines. The information on each study drug will be in accordance with approved submission documents.

5.3.1.1. Avelumab

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

5.3.1.2. Talazoparib

Talazoparib will be provided as capsules for oral administration. The 0.25 mg (Size 4 white) capsules will be supplied in bottles and labeled according to local regulatory requirements. Talazoparib is packaged in induction sealed, high density polyethylene bottles with child resistant caps of a single strength per bottle.

5.3.1.3. Bevacizumab

Bevacizumab is a sterile clear, colorless to pale brown solution for intravenous infusion. Each vial contains 400 mg of bevacizumab in 16 ml of solution and is intended for a single use in a single patient only.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

Pfizer GCS, WRD will provide either branded bevacizumab or biosimilar product.

5.3.1.4. Chemotherapy (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. Preparation and Dispensing

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

5.3.2.1. Preparation of Avelumab

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

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

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 study agents.

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

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

5.3.2.2. Dispensing of Talazoparib

Talazoparib should be dispensed on the Day 1 Visit of every cycle. A qualified staff member will dispense the investigational product in the bottles provided, in quantities sufficient to support dosing. The patient/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the investigational product away from children, and return the bottle to the site on the Day 1 Visit of the subsequent cycle.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the dispensing, handling, and safe disposal of talazoparib. Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment.[60] Patients should be advised that oral anti-cancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

5.3.2.3. Preparation of Bevacizumab

Bevacizumab to be administered during this study will be branded or biosimilar product available in the local region. Bevacizumab may be commercially available, and is to be stored, prepared, and administered according to locally approved product labeling or institutional guidelines.

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

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

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 study agents.

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

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

5.4. Administration of Chemotherapy Regimens

5.4.1. Paclitaxel and Carboplatin

5.4.1.1. 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.

5.4.1.1.1. 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 A chemotherapy period on the activity of avelumab is unknown (see Section 5.10.5).

5.4.1.1.2. 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.

5.4.1.2. Chemotherapy Regimen and Starting Doses

In the absence of progressive disease, patients will receive paclitaxel and carboplatin treatment for 6 cycles during the chemotherapy period of the study. Dose modifications for toxicity are allowed. 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.

5.4.1.2.1. Paclitaxel

Following pre medication, paclitaxel is administered as the first drug when chemotherapy is administered. For this study, paclitaxel will be administered at 175 mg/m^2 IV over 3 hours on Day 1 of each 3-week cycle.

5.4.1.2.2. Carboplatin

Carboplatin AUC 5 or AUC 6 is administered over 15-60 minutes (as per locally approved product labeling or institutional guidelines) after completion of the paclitaxel infusion on Day 1 of each 3-week chemotherapy cycle.

5.4.2. Administration of Avelumab Plus Chemotherapy

Avelumab will be administered by IV infusion at the investigational site. Avelumab will not be used for any purpose other than the trial.

For patients on Arm A, avelumab will be administered *after* chemotherapy as an 800 mg fixed dose via a 1-hour (-10/+20 minutes) IV infusion Q3W on Day 1 of each 3-week (21 day) chemotherapy cycle. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Avelumab premedication requirement is described in Section 5.5.1.2.

If premedication was administered prior to chemotherapy), the decision whether to repeat premedication prior to avelumab) is at the discretion of the investigator depending on the elapsed time and the half-life of corresponding premedication agent. 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 5.6.4 and Section 5.6.5.

5.4.3. Administration of Bevacizumab Plus Chemotherapy

For patients on Arm C, when both chemotherapy and bevacizumab are infused on Day 1 of each 3-week cycle during the chemotherapy period, bevacizumab will be infused after chemotherapy.

Bevacizumab 15 mg/kg will be administered intravenously once every 3 weeks starting on Day 1 of Cycle 2 in the chemotherapy period for adjuvant patients (may begin with Cycle 1 if surgery completed >4 weeks prior to randomization and no contraindications). For neoadjuvant patients, bevacizumab will be given on Day 1 of each 3-week cycle for Cycles 1, 2, 5 and 6 of the chemotherapy period.

5.5. Administration of Maintenance Therapies

Prior to starting treatment with talazoparib in the maintenance period and following the last dose of chemotherapy, patients must be re-evaluated for adequate renal function. Patients with a CL_{CR}>=60 mL/min will receive the starting dose of 0.75 mg talazoparib QD. For patients with moderate renal impairment (CL_{CR}=30-59 mL/min), the talazoparib starting dose should be reduced to 0.50 mg QD as per Section 5.6.1. All patients receiving talozoparib maintenance therapy should undergo routine renal function testing as per Section 7.1.4.

5.5.1. Avelumab Plus Talazoparib

During the maintenance period, on Days 1, 15, and 29 of each cycle, when both avelumab and talazoparib are administered at the investigative site, the following must occur in the order specified:

1. All required tests and assessments will be performed, as per the Schedule of Activities tables and blood will be drawn for PK and ADA assessments (when scheduled);

2. Avelumab premedication, as described below in Section 5.5.1.2, and talazoparib will be administered to the patient in any order chosen by the qualified site personnel;

3. Avelumab infusion will start after dosing with talazoparib;

4. Blood will be drawn for PK assessments (when scheduled) at the end of the avelumab infusion.

Effective with IRB/EC approval of amendment 2, treatment with avelumab and talazoparib will continue until disease progression is confirmed based on investigator assessment (except where treatment is allowed beyond progression, as per Section 5.7), unacceptable toxicity, or withdrawal of consent, whichever occurs first.

The investigational products and the required premedications are discussed in the following subsections, in the order of their administration.

5.5.1.1. Administration of Talazoparib

Talazoparib will be taken QD at 0.75 mg starting on Maintenance Cycle 1 Day 1 with or without avelumab (Arms A or B) and treatment should continue until End of Treatment/withdrawal. On Days 1, 15, and 29 of each maintenance cycle, when the patient returns to the clinic for avelumab administration, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and, for patients randomized to Arm A, before the avelumab infusion.

Patients should self-administer talazoparib orally QD, with or without food. The capsules should be swallowed whole with a glass of water without chewing, dissolving, or opening the capsules prior to swallowing.

Patients should be instructed to take talazoparib at approximately the same time each day and to not take more than the prescribed dose at any time.

If a patient misses a day of treatment or vomits any time after taking a dose, she must be instructed not to "make it up" but to resume subsequent doses the next day as prescribed.

Patients should complete the Dosing Diary after taking each dose. If the patient misses a day of treatment or takes a dose different than was prescribed, the reason for the missed dose or different dose must be recorded in the Dosing Diary. The Dosing Diary should be returned to the site at every cycle.

5.5.1.2. Premedication for Avelumab

In order to mitigate possible infusion related reactions from the administration of avelumab, patients have to be premedicated with an antihistamine and with acetaminophen (paracetamol) or according to local institutional clinical guidelines prior to the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

When avelumab and talazoparib are administered on the same day, premedications may be given either prior to talazoparib, at the same time as talazoparib, or after talazoparib. However, the avelumab infusion will not start until after talazoparib and after the avelumab premedication was administered.

5.5.1.3. Administration of Avelumab

Avelumab will be administered by IV infusion at the investigational site.

Avelumab will be administered as an 800 mg fixed dose via a 1-hour (-10/+20 minutes) IV infusion Q2W on Day 1, Day 15, and Day 29 of each 42-day maintenance cycle (6 week cycle). Patients should be instructed to report any delayed reactions to the Investigator immediately.

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

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

5.5.1.3.1. Special Precautions for the Administration of Avelumab

As with all mAb 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.

If an allergic reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms of avelumab infusion related reactions include, but are not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Management of avelumab infusion related reactions is described in Section 5.6.4.

5.5.1.4. Food Requirements

Both investigational products may be administered without regard to food.

5.5.2. Administration of Bevacizumab

Bevacizumab to be administered during this study will be branded or biosimilar product available in the local region. Bevacizumab may be commercially available, and is to be stored, prepared, and administered according to locally approved product labeling or institutional guidelines.

Bevacizumab 15 mg/kg will be administered intravenously on Days 1 and 22 of each 6-week maintenance cycle. The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Patient weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. If a patient's weight changes by ≥10% during the course of the study, then the bevacizumab dose will be recalculated.

5.6. Recommended Dose Modifications and Toxicity Management

Every effort should be made to administer each investigational product at the planned dose and schedule.

In the event of significant toxicity, dosing may be interrupted, delayed, and/or reduced, only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Investigators determine if an AE is attributed to one or more IP in combination treatment and the treatment/dose modifications may occur independently for each investigational product in the combination based on the general guidance, as follows:

- Avelumab: No dose reductions are permitted in this study, but the next infusion may be omitted based on persisting toxicity.
- Talazoparib: Dose modifications (dose interruptions or dose reductions) may be implemented to manage toxicities.
- Bevacizumab: There will be no dose reduction for Bevacizumab. Treatment should be interrupted or discontinued for certain adverse events. Dose modification (dose delays or omissions) for bevacizumab due to adverse drug reactions (ADRs) should be made in accordance with the guidance provided below, product labeling and/or institutional guidelines.

See sections below for details regarding the specific protocol permitted modifications for each investigational product.

All dose modifications must be clearly documented in the patient's medical chart and in the CRF.

In addition to dose modifications, Investigators are encouraged to employ best supportive care according to local institutional clinical practices.

5.6.1. Dose Reductions for Talazoparib

Following dosing interruption due to toxicity at any time in the study, the talazoparib dose may need to be reduced, based on the worst toxicity reported, when treatment is resumed. Dose reduction should be made in accordance with the guidance provided below in Section 5.6.2. Dose reduction of talazoparib by 1 dose level at a time will be allowed depending on the starting dose and type and severity of toxicity encountered. Patients unable to tolerate 0.25 mg QD, will be permanently discontinued from the talazoparib, but may

continue on single agent avelumab if on Arm A. Available dose levels for dose reductions are listed in Table 4.

Table 4. Dose Levels for Dose Reductions of Talazoparib

Dose Level	Talazoparib Dose (Oral)
Starting	0.75 mg QD
Dose level -1	0.50 mg QD
Dose Level -2	0.25 mg QD

Talazoparib dose de-escalation below 0.25 mg QD is not allowed.
D = dose; QD = every day

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Intra patient dose re escalation is not allowed.

Recommended dose reductions for talazoparib are described in Section 5.6.2.

5.6.2. Study Treatment Modifications for Drug-related Toxicity from Avelumab and Talazoparib (Excluding Infusion-Related Reactions and Immune-Related Adverse Events)

Recommended treatment modifications avelumab and talazoparib in case of investigational product related toxicity are shown in Table 5. The specific guidelines are applicable in cases which can be attributed to one of the investigational products. The instructions should be followed in the column regarding the investigational product that toxicity is attributed to. In cases where an AE is possibly related to both investigational products, the guidelines in both columns for both investigational products should be followed. Patients who stop avelumab or talazoparib for unacceptable toxicity may continue treatment with the investigational product that is not considered to be responsible for the toxicity observed.

Avelumab infusion related reactions should be managed according to guidelines in Section 5.6.4.

For patients receiving avelumab in combination with talazoparib, any AE suspected to be immune related should be managed according to the guidance for management of irAEs in Section 5.6.5.

Table 5. Talazoparib and Avelumab Treatment Modifications for Drug-Related Toxicity (Excluding Infusion-Related Reactions and Immune-Related AEs)

	Talazoparib	Avelumab
Hematologic toxicities		
Grade 1 and Grade 2	• No requirement for dose interruption or dose reduction.	• Continue as per schedule.
Anemia Grade ≥3 (hemoglobin <8 g/dL)	• Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until until hemoglobin returns to 9 g/dL or better. Then resume talazoparib at a reduced dose at the initiation of the next cycle. • If anemia with hgb <8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL (Day 1), then resume talazoparib at a further reduced dose at the initiation of the next cycle. • If anemia persists for >4 weeks without recovery of hemoglobin to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.	• Hold avelumab. • Re-initiate avelumab once hemoglobin ≥8 g/dL or baseline. • Permanently discontinue avelumab if hemoglobin does not return to 8g/dL within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).
Neutropenia Grade ≥3 (ANC <1000/μL)	• Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL. Then resume talazoparib at a reduced dose at the initiation of the next cycle. • If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥1500/μL, then resume talazoparib at a further reduced dose at the initiation of the next cycle. • If neutropenia persists for >4 weeks without recovery to ≥1500/μL at any dose level despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. G-CSF and GM-CSF may be used at investigators discretion for the supportive treatment of neutropenia at any occurence.	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 (ANC ≥1500/μL) or baseline. • Permanently discontinue avelumab if toxicity does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).

Table 5. Talazoparib and Avelumab Treatment Modifications for Drug-Related Toxicity (Excluding Infusion-Related Reactions and Immune-Related AEs)

	Talazoparib	Avelumab
Thrombocytopenia Grade ≥3 (platelets <50,000/μL)	• Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥50,000/μL, then then resume talazoparib at a reduced dose at the initiation of the next cycle. • If thrombocytopenia (<50,000/μL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥75,000/μL, then resume talazoparib a further reduced dose at the initiation of the next cycle. • If thrombocytopenia persists for >4 weeks without recovery to ≥50,000/μL despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at investigators discretion for the supportive treatment of thrombocytopenia at any occurrence.	• Hold avelumab. • Re-initiate avelumab once platelets ≥50,000/μL. • Permanently discontinue avelumab if toxicity does not resolve to ≥50,000/μL within 12 weeks or if the same Grade 3 toxicity recurs (if talazoparib had already been discontinued and recurrent event occurs on avelumab only).
Non-hematologic toxicities		
Grade 1 and Grade 2	• No requirement for dose interruption or dose reduction. • For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 5.6.5, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.	• Continue as per schedule. • For suspected immune-related toxicities due to avelumab follow guidance in Section 5.6.5.

Grade 3	• Hold talazoparib.
	• Resume talazoparib reduced by 1 dose level, per Section 5.6.1 if toxicity resolves to Grade ≤1 or baseline within 4 weeks.
	  • **Exceptions are:** Nausea, vomiting, or diarrhea lasting ≤72 hours; fatigue lasting <5 days; hypertension controlled with medical therapy; increase in indirect bilirubin indicative of Gilbert's syndrome; serum lipase or amylase lasting ≤7 consecutive days without clinical signs or symptoms of pancreatitis; endocrinopathies controlled with hormonal therapy; laboratory values that
		• Hold avelumab.
		• Resume once toxicity is Grade ≤1 or baseline.
		• Permanently discontinue if toxicities does not resolve to Grade ≤1 or baseline within 12 weeks or if the same Grade 3 toxicity recurs:
		  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
		• For suspected immune-related toxicities follow guidance in Section 5.6.5.

Table 5. Talazoparib and Avelumab Treatment Modifications for Drug-Related Toxicity (Excluding Infusion-Related Reactions and Immune-Related AEs)

	Talazoparib	Avelumab
	do not have any clinical correlate. • If the same Grade 3 toxicity recurs, reduce by 1 dose level. • Permanently discontinue if toxicity does not improve to Grade ≤1 or baseline within 4 weeks. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • Permanently discontinue if Grade 3 liver test abnormality. Rechallenge may be considered once toxicity is Grade ≤1 or baseline, if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is identified. • For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 5.6.5, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.	

Grade 4	• Permanently discontinue talazoparib:
	  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
		• Permanently discontinue avelumab.
		  • **Exceptions are:** Laboratory values that do not have any clinical correlate.
		• For suspected immune-related toxicities follow guidance in Section 5.6.5.

Abbreviations: AML=Acute Myeloid Leukemia; ANC=Absolute Neutrophil Count; MDS=Myelodysplastic Syndrome.		

5.6.3. Overdose of Talazoparib

There is no specific treatment in the event of talazoparib overdose, and symptoms of overdose are not established. In the event of overdose, treatment with talazoparib should be stopped, and physicians should consider gastric decontamination, follow supportive measures, and treat symptomatically.

5.6.4. Treatment Modifications for Infusion-Related Reactions Associated with Avelumab

Recommended treatment modifications in case of avelumab infusion related reactions are shown in Table 6.

Table 6. Treatment Modification for Symptoms of Infusion-related Reactions Associated With Avelumab

NCI CTCAE Severity Grade	Treatment Modification
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids; prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume avelumab infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.[a] • If a Grade 2 infusion related reaction does not improve or worsens following the decrease in infusion rate and appropriate symptomatic treatment the infusion should not be resumed for that day.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion tubing from the subject. • Patients have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

a. If avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at subsequent infusions.

Abbreviations: NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs; IV=intravenous.

If, in the event of a Grade 2 infusion related reaction that does not improve or worsens after implementation of the modifications indicated above (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.

5.6.5. Immune-Related Adverse Events Toxicity Management

For patients receiving avelumab in combination with talazoparib, any AE suspected to be immune-related (ie, an irAE) should be managed according to the guidance for management of irAEs (see Table 7) below.

Treatment of irAEs is mainly dependent on 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 Grades 3 to 4 AE.

- Grades 3 to 4: treat with high dose corticosteroids; if suspected to be related to avelumab, talazoparib should be withhold until toxicity resolves to Grade ≤1 or baseline.

For Grade ≥3 immune related toxicities suspected to be related to avelumab, talazoparib should be withheld until toxicity resolves to Grade ≤1 or baseline.

Table 7. Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 • **Diarrhea:** <4 stools/day over Baseline. • **Colitis:** asymptomatic.	• Continue avelumab therapy. • Symptomatic treatment (eg, loperamide).	• Close monitoring for worsening symptoms. • Educate subject to report worsening immediately. • If worsens, treat as Grade 2, 3 or 4.
Grade 2 • **Diarrhea:** 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL. • **Colitis:** abdominal pain; blood in stool.	• Withhold avelumab therapy. • Symptomatic treatment.	• If improves to Grade ≤1, resume avelumab therapy. • If persists >5-7 days or recurs, treat as Grade 3 or 4.
Grade 3 to 4 • **Diarrhea (Grade 3):** ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL. • **Colitis (Grade 3):** severe abdominal pain, medical intervention indicated, peritoneal signs. • **Grade 4:** life-threatening, perforation.	• Withhold avelumab for Grade 3. • Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. • 1.0-2.0 mg/kg/day prednisone IV or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider lower endoscopy.	• If improves, continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). • If worsens, persists >3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contraindication). *Note: infliximab should not be used in cases of perforation or sepsis.*

Table 7. Management of Immune-Related Adverse Events

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area.	• Continue avelumab therapy. • Symptomatic therapy (for example, antihistamines, topical steroids).	• If Grade 2 persists >1 to 2 weeks or recurs, withhold avelumab therapy. • Consider skin biopsy. • Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. • If worsens, treat as Grade 3 to 4.
Grade 3 to 4 • **Grade 3:** Covering >30% body surface area. • **Grade 4:** Life threatening consequences.	• Withhold avelumab for Grade 3. • Permanently discontinue for Grade 4 or recurrent Grade 3. • Consider skin biopsy. • Dermatology consult. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections.	• If improves to Grade ≤1, taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only.	• Consider withholding avelumab therapy. • Monitor for symptoms every 2 -3 days. • Consider Pulmonary and Infectious Disease consults.	• Re-assess at least every 3 weeks. • If worsens, treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms.	• Withhold avelumab therapy. • Pulmonary and Infectious Disease consults. • Monitor symptoms daily; consider hospitalization. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for	• Re-assess every 1 to 3 days. • If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids

Table 7. Management of Immune-Related Adverse Events

	opportunistic infections. • Consider bronchoscopy, lung biopsy.	taper. • If not improving after 2 weeks or worsening, treat as Grade 3 to 4.
Grade 3 to 4 • **Grade 3**: Severe new symptoms; New/worsening hypoxia; • **Grade 4:** Life-threatening.	• Permanently discontinue avelumab therapy. • Hospitalize. • Pulmonary and Infectious Disease consults. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider bronchoscopy, lung biopsy.	If improves to Grade ≤1, taper steroids over at least 1 month. If not improving after 48 hours or worsening, add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil).
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 • Grade 1 AST or ALT >ULN to 3.0 x ULN; • and/or Total bilirubin >ULN to 1.5 x ULN.	• Continue avelumab therapy.	• Continue liver function monitoring • If worsens, treat as Grade 2 or 3 to 4.
Grade 2 • AST or ALT >3.0 to ≤5 x ULN; • and/or total bilirubin >1.5 to ≤3 x ULN.	• Withhold avelumab therapy. • Increase frequency of monitoring to every 3 days.	• If returns to Grade ≤1, resume routine monitoring; resume avelumab therapy. • If elevation persists >5 to 7 days or worsens, treat as Grade 3 to 4.
Grade 3 to 4 • AST or ALT >5 x ULN; • and/or total bilirubin >3 x ULN.	• Permanently discontinue avelumab therapy. • Increase frequency of monitoring to every 1 to 2 days. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consult gastroenterologist/ hepatologist. • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	• If returns to Grade ≤1, taper steroids over at least 1 month. • If does not improve in >3 to 5 days, worsens or rebounds, add mycophenolate mofetil 1 gram (g) twice daily. • If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Table 7. Management of Immune-Related Adverse Events

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN to 1.5 x ULN.	• Continue avelumab therapy.	• Continue renal function monitoring. • If worsens, treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased >1.5 and ≤6 x ULN.	• Withhold avelumab therapy. • Increase frequency of monitoring to every 3 days. • Add prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • 1.0-2.0 mg/kg/day prednisone or equivalent.	• If returns to Grade ≤1, taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. • If worsens, treat as Grade 4.
Grade 4 Creatinine increased >6 x ULN.	• Permanently discontinue avelumab therapy. • Monitor creatinine daily. • 1.0 to 2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • Nephrology consultation.	• If returns to Grade ≤1, taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
• New onset of cardiac signs or symptoms. • and / or new laboratory cardiac biomarker elevations (eg, troponin, CK-MB, BNP). • or cardiac imaging abnormalities suggestive of myocarditis.	• Withhold avelumab therapy. • Hospitalize. • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. • Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. • Guideline based supportive treatment as per cardiology consult.* • Consider myocardial biopsy if recommended per cardiology consult.	• If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. • If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	• Permanently discontinue avelumab. • Guideline based supportive treatment as appropriate as per cardiology consult.* • 1.0-2.0 mg/kg/day prednisone or	• Once improving, taper steroids over at least 1 month. • If no improvement or worsening, consider

Table 7. Management of Immune-Related Adverse Events

	equivalent. • Add prophylactic antibiotics for opportunistic infections.	additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001.		
Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Continue avelumab therapy. • Endocrinology consult if needed. • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	• Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Withhold avelumab therapy. • Consider hospitalization. • Endocrinology consult. • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. • Rule-out secondary endocrinopathies (ie, hypopituitarism/hypophysitis).	• Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression). • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women). • Hormone replacement/suppressive therapy as appropriate. • Perform pituitary MRI and visual field examination as indicated. If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in	• Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). • In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. • Continue hormone replacement/suppression therapy as appropriate.

Table 7. Management of Immune-Related Adverse Events

	1 month. • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. • Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	• Withhold avelumab therapy pending clinical investigation.	• If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy. • If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	• Withhold avelumab therapy. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Specialty consult as appropriate.	• If improves to Grade ≤1, taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	• Permanently discontinue avelumab therapy. • 1.0-2.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Specialty consult as appropriate.	• If improves to Grade ≤1, taper steroids over at least 1 month.
Grade 4	• Permanently discontinue avelumab therapy. • 1.0-2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed. • Add prophylactic antibiotics for opportunistic infections. • Specialty consult.	• If improves to Grade ≤1, taper steroids over at least 1 month.
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency. Persistent Grade 2 or 3 irAE lasting 12 weeks or	• Permanently discontinue avelumab therapy. • Specialty consult.	

Table 7. Management of Immune-Related Adverse Events

longer.		

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

5.6.6. Guidelines for Toxicity Management Bevacizumab

Dose modification (dose delays and omissions) for bevacizumab due to ADRs should be made in accordance with the guidance provided in Table 8, product labeling and/or institutional guidelines.

Table 8. Bevacizumab Treatment Modifications for Drug-Related Toxicity

Permanently discontinue bevacizumab for:
Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ.
Wound dehiscence and wound healing complications requiring medical intervention.
Serious hemorrhage (ie, requiring medical intervention).
Severe arterial thromboembolic events.
Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism.
Hypertensive crisis or hypertensive encephalopathy.
Posterior Reversible Encephalopathy Syndrome (PRES).
Nephrotic syndrome.
Temporarily suspend bevacizumab for:
At least 4 weeks prior to elective surgery.
Severe hypertension not controlled with medical management.
Moderate to severe proteinuria.
Severe infusion reaction.

5.6.7. Guidelines for Toxicity Management Chemotherapy

Dose modification (dose delays and dose change) for carboplatin/paclitaxel due to ADRs should be made in accordance with the product labeling and institutional guidelines or with the guidance provided in the sections below. There will be no substitutions for paclitaxel or carboplatin in the management of any toxicities. Starting doses for carboplatin and paclitaxel and dose reduction levels are described in Table 10.

5.6.7.1. 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 A) 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.

5.6.7.2. Modifications for Hematologic Toxicities

There will be no paclitaxel dose reductions based on hematologic toxicity.

Initial occurrence of dose limiting neutropenia or dose limiting thrombocytopenia will be managed according to 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, **or** ANC <1000 cells/μl on Day 1.
- 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, **or** platelet count of <75,000/μl on Day 1. There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

Table 9. Modification Guidance for Hematologic Toxicity

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

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

5.6.7.3.1. Renal Toxicity

The combination of carboplatin and paclitaxel with 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.

5.6.7.3.2. 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 5.6.5 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.

5.6.7.3.3. 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.

5.6.7.3.4. 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.

5.6.7.3.5. Hypersensitivity to Paclitaxel

A hypersensitivity reaction to paclitaxel is not a dose limiting toxicity. The acute management should occur as per local practice, however, there will be no substitutions allowed.

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.

5.6.7.3.6. Hypersensitivity to Carboplatin

If there is a hypersensitivity reaction to carboplatin, then this should be managed as per local institutional protocols, however, there will be no substitutions allowed.

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.

5.6.7.3.7. Other Toxicities of Chemotherapy

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 chemotherapy treatment, treatment should be withheld until recovery to Grade ≤1 and subsequent treatment should be reduced by one dose level (see Table 10).

5.6.8. Dose Modifications for Chemotherapy Combinations

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 10. Dose Modification Levels for Paclitaxel and Carboplatin

Drug	Starting Dose	Dose Level 1	Dose Level 2
Paclitaxel Q3W	175 mg/m2	135 mg/m2	110 mg/m2
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.

5.6.8.1. Dose Modifications for Avelumab in Combination with Chemotherapy (Arm A)

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

For patients on Arm A (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 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 11 for guidance on management of toxicities in the combination treatment arm (Arm A) during the chemotherapy period.

For any other adverse event not covered in Table 11 below, see Section 5.6 for relevant avelumab toxicity management guidelines and refer to local product label and standard institutional guidelines or guidance provided in the protocol for chemotherapy toxicity management (Section 5.6.7).

Table 11. Avelumab in Combination With Chemotherapy (Arm A) Toxicity Management

Toxicity	Treatment Modification for Chemotherapy	Treatment Modification for Avelumab
Hematologic toxicity	See Section 5.6.7.2.	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 5.6.5) 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 5.6.5 and Table 7.

Table 11. Avelumab in Combination With Chemotherapy (Arm A) Toxicity Management

Toxicity	Treatment Modification for Chemotherapy	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 5.6.7.3.3).	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 5.6.7.3.4.	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 5.6.7.3.5 and Section 5.6.7.3.6.	See Section 5.6.2 and Table 7.

5.6.8.2. Dose Modifications for Bevacizumab in Combination with Chemotherapy (Arm C)

For Bevacizumab, no dose reductions are permitted in this study, but doses may be delayed or omitted based on persisting toxicity, as described for bevacizumab in Section 5.6.6 and for chemotherapy management in Section 5.6.7.

In the event of significant toxicity during the chemotherapy induction period, all treatment will be delayed (including Bevacizumab) until recovery. If dose modifications are required for patients to continue therapy, only the chemotherapy will be reduced as described in Section 5.6.8. Patients who fail to recover within reasonable time (3 weeks) or despite two carboplatin and/or paclitaxel dose reductions will no longer receive protocol directed chemotherapy but bevacizumab can be continued, provided absence of any contraindication.

5.7. Treatment after Initial Evidence of Radiological Disease Progression (Only for Patients on Arm A in Maintenance Period)

Immunotherapeutic agents such as avelumab may produce antitumor effects by potentiating cancer-specific immune responses. Following immunotherapy, a clinical response may occur later than would typically be expected following treatment with a cytotoxic agent. In addition, this response may occur after an initial increase in tumor burden or even after the appearance of new lesions.

If radiologic imaging shows disease progression, and if in Investigator's clinical judgement the patient is still experiencing clinical benefit, the patient may be eligible for continued treatment with avelumab if the following criteria are met:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease by radiographic imaging;
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

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

If repeat imaging does not confirm PD, treatment with avelumab and talazoparib may be continued.

If the repeat imaging confirms PD, patients should be considered for discontinuation from all investigational products. However, according to the Investigator's clinical judgment and after discussion between the Investigator and the Sponsor, if a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with 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.

Effective with IRB/EC approval of amendment 2, if the patient is subsequently found to have further disease progression as assessed by investigator, then treatment with all investigational products should be permanently discontinued.

5.8. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, 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 products should be stored in their original containers and in accordance with the labels. See the IP manual for storage conditions of the products.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.9. Investigational Product Accountability

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

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.

All unused talazoparib must be returned to the Investigator or designated investigative site personnel by each patient on Day 1 of every cycle and at the end of the trial in order to perform and document drug accountability.

5.9.1. 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 investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.10. Concomitant Treatment(s)

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 corticosteroids use see Section 5.10.5.

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

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

Effective with IRB/EC approval of protocol amendment 2, concomitant medications and treatments will not be captured in the INFORM database unless these medications contribute or are associated with the treatment for an AE/SAE. However, this information should be recorded in the patient's source documents.

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

Recommended medications to treat infusion related reactions, and hypersensitivity reactions, and immune related events are reported in Section 5.6.4, and Section 5.6.5, respectively.

5.10.1. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline; otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

Study treatment should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion. Effective with IRB/EC approval of Amendment 2, concomitant radiotherapy data will not be captured in the INFORM database. This information should be recorded in the patient's source documents.

5.10.2. Concomitant Surgery

Effective with IRB/EC approval of Amendment 2, concomitant surgey data will not be captured in the INFORM database. This information should be recorded in the patient's source documents.

5.10.2.1. Interval Debulking Surgery

Effective with IRB/EC approval of Amendment 2, interval debulking surgery may be performed according to local guidelines or standard of care at the discretion of the investigator. This information should be recorded in the patient's source documents.

Patients who are enrolled prior to initiation of neoadjuvant therapy will complete 3 cycles of chemotherapy, treatment will be held, and patients will proceed to have interval debulking surgery. Upon recovery from surgery, the remaining duration of chemotherapy should be administered according to local institutional practice.

For neoadjuvant patients in Arm C, bevacizumab treatment will not be administered with chemotherapy on cycles before (Cycle 3) and after (Cycle 4) IDS due to concerns about its impact on potential wound healing complications.

Patients who cannot undergo planned interval debulking surgery at all are allowed to continue treatment per protocol provided no disease progression.

5.10.2.2. Other Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. There is no evidence suggesting that treatment with avelumab increases surgical risk.

The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. In case of a surgical procedure, investigational products should be delayed. Postoperatively, the decision to reinitiate investigational products should be discussed with the Sponsor.

5.10.3. Hematopoietic Growth Factors

It is anticipated that myelosuppression may be a significant side effect of chemotherapy. These factors may be used at any time to treat emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines[61] or as allowed per local guidance. Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

5.10.4. Bisphosphonates or Denosumab

Bisphosphonate or denosumab treatment is allowed and it will be given as per local practice. The need to initiate treatment with bisphosphonate or denosumab or to increase the dose of these therapies while on study treatment (for patients who started bisphosphonate or denosumab therapy >2 weeks before study enrollment), may be considered as a symptom of disease progression that should be confirmed radiologically.

5.10.5. Corticosteroids

Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[62,63] 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 avelumab. However, studies with anti-CTLA-4 compounds indicate that short-term use of steroids can be employed without compromising clinical outcomes.[64] Therapeutic and/or prophylactic corticosteroids may be used as needed per standard of care.

5.10.6. Other Prohibited Concomitant Medicines and Therapies

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

- Any anti-cancer systemic chemotherapy or biological therapy, including vitamins that are used as anti-cancer treatments, other than avelumab and talazoparib.
- Immunotherapy not specified in this protocol.
- Investigational agents other than avelumab, talazoparib, and bevacizumab where considered investigational.

- Radiation therapy (with the exception noted above in the Concomitant Radiotherapy Section 5.10.1).

- Other experimental pharmaceutical products.

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

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

- The following strong P-gp inhibitors that result in ≥2-fold increase in the exposure of in vivo probe P-gp substrates according to the University of Washington Drug-Drug Interaction database[89] are prohibited while on talazoparib treatment: amiodarone, carvedilol, clarithromycin, cobicistat, darunavir, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinvir, telaprevir, tipranavir, valspodar, and verapamil.

- P-gp inducers including, but not limited to avasimibe, carbamazepine, phenytoin, rifampin, and St. John's Wort are prohibited while on talazoparib treatment.

- BCRP inhibitors including, but not limited to curcumin, cyclosporine, elacridar [GF120918], and eltrombopag are prohibited while on talazoparib treatment.

There are no prohibited therapies during the 90-day Follow-Up period.

5.10.7. Cautionary Use of Concomitant Medicines While on Treatment with Talazoparib

Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of the following transporter inhibitors with talazoparib: atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract.

5.11. Rescue Medication and Supportive Care

5.11.1. Supportive Care Guidelines

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

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

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

- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice, assuming there is no expected drug-drug interaction with study treatments (see Section 5.10.6 and Section 5.10.7). Prophylactic administration should be considered for the cases outlined in Table 7.

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

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

6. STUDY PROCEDURES

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

6.1. Screening (Obsolete)

Enrollment was stopped, and patients can no longer be screened as of 19 March 2019. Please refer to the new SOA in Appendix 6.

To allow for additional flexibility in scheduling patient visit and procedures, Screening and Cycle 1 Day 1 procedures (except for tumor scans) may be completed on the same day for all treatment arms. However, screening assessments for eligibility MUST have already been completed before the patient is randomized. No re-screening will be permitted in this study.

Following informed consent, patients who are screened for treatment, and who do not have an existing test result for gBRCA1/2 defect status must provide a 10 mL of blood sample for testing during screening to enable stratification of randomization based on germline BRCA1/2 mutational status. For patients with an existing test result for germline BRCA1/2 defect status, test result must have been obtained using a CLIA (or comparable local validation) approved assay.

Once completion of screening assessments and eligibility is confirmed, patients will subsequently be randomized to 1 of the 3 treatment arms for the study. Treatment must start within 3 days after randomization.

Patients will be asked about any baseline signs and symptoms experienced within the 28 days prior to randomization and any findings will be recorded on the Medical History CRF page. After randomization, any new or worsening conditions since baseline should be reported on the AE CRF.

6.2. Treatment Period

The study period includes two treatment periods, the chemotherapy period and the maintenance period. For the purpose of scheduling evaluations, providing clarity on assessments, and consistent on-treatment assessments across all three treatment arms, the definition of cycle length varies between the chemotherapy period and the maintenance period. In the chemotherapy period, a cycle is defined as 3 weeks (21 days), and due to the biweekly schedule of avelumab and the Q3W schedule for bevacizumab, a cycle in the maintenance period is defined as 6 weeks (42 days).

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 treatment period procedures, please refer to the new SOA in Appendix 6.

During the chemotherapy period, patients on all arms will continue with the chemotherapy treatment for up to 6 cycles until objective progression of disease based on investigator assessment that the patient is no longer receiving clinical benefit, unacceptable toxicity, consent withdrawal, or death whichever comes first.

Prior to treatment with talazoparib in the maintenance period, patients must be evaluated for adequate renal function, and those with moderate renal impairment (30-59 mL/min) will receive a reduced starting dose of 0.50 mg for talazoparib (see Section 5.5).

During the maintenance period of the study, patients receiving talazoparib with or without avelumab (Arms A or B) will continue treatment until progression of disease based on investigator assessment that the patient is no longer receiving clinical benefit, unacceptable toxicity, consent withdrawal, a maximum duration of 24 months (not including chemotherapy period), or death, whichever comes first. Patients receiving bevacizumab (Arm C), will continue maintenance treatment until progression of disease based on investigator assessment that the patient is no longer receiving clinical benefit, unacceptable toxicity, consent withdrawal, a maximum duration of 21 or 22 doses, per local approval (including chemotherapy period), or death, whichever comes first.

For patients randomized to Arms A or B, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and, for patients randomized to Arm A, before the infusion of avelumab.

6.3. End of Treatment

For End of Treatment procedures, see the Appendix 6 tables and ASSESSMENTS sections.

Patients will receive study treatment until progressive disease based on investigator assessment, unacceptable toxicity, a determination that the patient is no longer receiving clinical benefit, withdrawal of consent, or death whichever comes first. 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.

6.4. 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 (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Reasons for withdrawal from the study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.7 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to 1 of the investigational products, the Investigator may continue treatment with the other investigational product(s);
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Refused further follow-up;
- Study terminated by Sponsor;
- Death.

Reasons for withdrawal from the study may include:

- Study terminated by Sponsor;
- Lost to follow-up;

- Refused further follow-up;
- Death.

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

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. See additional details in Section 6.4.1 below.

6.4.1. Withdrawal of Consent

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product (in which case the withdrawal of consent form is not applicable) or also from study procedures and/or posttreatment study follow-up (in which case a withdrawal of consent form should be provided and signed). In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.4.2. 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. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

6.5. Short-Term Follow-Up

For follow-up procedures see the updated SOA in Appendix 6.

In short-term follow-up, patients should be evaluated for safety through 90 days (at 30 days, 60 days, and 90 days) after last dose of investigational product(s).

7. ASSESSMENTS

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

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

7.1. Safety Assessments

Effective with IRB/EC approval of Amendment 2, safety assessments will include collection of AEs, SAEs, vital signs, laboratory assessments, including pregnancy tests, and verification of concomitant treatments. Physical examination and electrocardiogram (ECG) are not required per protocol but may be performed as clinically necessary.

Please see Appendix 6 for the updated SOA for safety requirements.

7.1.1. Pregnancy Testing

For patients of childbearing potential, a serum or urine pregnancy test, with a 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 study treatment 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 study treatment. Pregnancy tests will also be routinely repeated at Day 1 of each chemotherapy cycles, Day 1 and Day 29 (Arms A and B) and Day 1 and Day 22 (Arm C) of maintence treatment, and at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study. See also Appendix 6 tables for each arm.

7.1.2. Contraception Check

The Investigator or his or her desigee will discuss and confirm that any fertile female patients who are of childbearing potential, who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception (See Section 4.3). The Investigator or his or her designee will discuss with the patient the need to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency) consistently and correctly throughout the study 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. Patients who are, in the opinion of the Investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of contraception (at least one of which is considered to be highly effective with low user dependency) throughout the study or for at least 30 days after the last dose of avelumab, 7 months after the last dose of talazoparib, and for 6 months after the last dose of bevacizumab, whichever is longer. See also Appendix 6 tables for each arm.

7.1.3. Adverse Events

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

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 Table 7 Avelumab Management of Immune Related Adverse Events. AESIs are reported according to the general AE reporting rules specified in Section 8.1.

7.1.4. Laboratory Safety Assessments

Effective with IRB/EC approval of Amendment 2, samples for all laboratory assessments will be drawn at the time points indicated in the updated SOA Appendix 6 for details on sample timings for each arm and when clinically indicated and do not need to be recorded in the INFORM database, unless the findings support an AE/SAE. Repeat samples do not have to be drawn on Cycle 1 Day 1 if these samples were drawn in the prior 3 days. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. Results from pregnancy tests, if taken, must be available for review prior to dosing. Samples will be analysed at local laboratories.

Hematology and blood chemistry must be drawn prior to the administration of study treatment dose at the time points described in the SOA Appendix 6 table for each arm and analyzed at local laboratories. Hemoglobin, platelets, absolute neutrophil count, creatinine, AST and ALT results must be reviewed by the treating physician prior to infusion of chemotherapy and/or avelumab. They may also be performed when clinically indicated. The required laboratory tests are listed in Table 12.

Table 12. Required Safety Laboratory Tests

Hematology	**Chemistry Panel**
Hemoglobin	ALT
Platelets	AST
WBC	Alkaline Phosphatase
Absolute Neutrophils	Sodium
	Potassium
	Total Bilirubin
Thyroid Function Tests	BUN or Urea
Free T4	Creatinine
TSH	Uric Acid (for leukemia and lymphomas)
	Glucose (non-fasted)
Pregnancy Test	Albumin
For female patients of childbearing potential, serum or urine	Phosphorous or Phosphate
	Creatine kinase
	Gamma glutamyltransferase

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, TSH=thyroid-stimulating hormone, WBC=white blood cell

Effective with IRB/EC approval of Amendment 2, urinalysis is to be conducted for patients in Arm C on Day 1 of every treatment cycle, and Day 22 of every maintenance cycle, and end of treatment. If the results of the dipstick urine protein indicate ≥2+ proteinuria, follow-up should be performed with a quantitative urine protein analysis according to local standard practices with data captured on the AE CRF if AE criteria are met.

Adequate renal function by estimated creatinine clearance as calculated using the Cockcroft Gault method or by 24 hour urine collection for creatinine clearance or according to local institutional standard method will be conducted on Day 1 of every treatment cycle.

7.1.5. Vital Signs and Physical Examination

Effective with IRB/EC approval of Amendment 2, vital signs including weight, height, blood pressure, temperature, and pulse rate are to be performed per SOA in Appendix 6. These data do not need to be recorded in the INFORM database, unless the findings support an AE/SAE.

Effective with IRB/EC approval of Amendment 2, physical examination and ECOG performance status are not required per protocol, but may be performed as clinically necessary. These data do not need to be recorded in the INFORM database, unless the findings support an AE/SAE. Clinically significant findings must be reported as AEs.

7.1.6. Electrocardiogram Assessments

Effective with IRB/EC approval of Amendment 2, ECG assessments are not required per protocol but may be performed as clinically necessary. These data do not need to be recorded in the INFORM database, unless the findings support an AE/SAE.

The remainder of this section is obsolete.

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, prior to the start of treatment (Cycle 1 Day 1) and at the end of treatment/withdrawal of the maintenance period. Additional 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 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. Pharmacokinetic Assessments (Obsolete)

Effective with IRB/EC approval of Amendment 2, PK assessments will no longer be collected.

PK sampling schedule may be modified based on emerging PK data. Blood for PK samples will be drawn from the arm contralateral to the drug infusion.

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, with the exception of samples where nominal time coincides with end of infusion, samples obtained within ±10% of the nominal time (eg, within 3 minutes of a 30 minute sample) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). For samples where nominal time coincides with end of infusion, a sample collected within 10 min post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If the infusion of avelumab is interrupted due to AE, any PK samples scheduled during the time the AE is occurring are not required. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of clinical investigators, patient and Sponsor.

PK samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

Details regarding the collection, processing, storage and shipping of the PK blood samples will be provided to the investigator site prior to initiation of the trial. The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping

conditions), including any actions taken, must be documented and reported to the Sponsor. On a case by case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

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7.2.1. Blood for PK Analysis of Avelumab (Obsolete)

Effective with IRB/EC approval of Amendment 2, blood samples for PK analysis of avelumab will no longer be collected.

Blood samples (3.5 mL whole blood at each time point) will be collected for PK analysis of avelumab into an appropriately labeled serum separator tube (SST), as outlined in the Schedule of Activities table for Arm A. Pre-dose avelumab PK samples will be collected within 1 hour prior to taking talazoparib dose and the post-dose avelumab PK samples should be taken within 10 minutes after the avelumab infusion ends. Blood for PK samples will be drawn from the contralateral arm of the drug infusion. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

7.2.2. Blood for PK Analysis of Talazoparib (Obsolete)

Effective with IRB/EC approval of Amendment 2, blood samples for PK analysis of talazoparib will no longer be collected.

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of talazoparib into an appropriately labeled tube as outlined in Schedule of Activities table for Arms A and B. Pre-dose talazoparib PK samples will be collected within 1 hour prior to taking talazoparib dose. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

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7.4. CCI [redacted] Pharmacodynamic Assessments (Obsolete)

Effective with IRB/EC approval of Amendment 2, CCI [redacted] and pharmacodynamic assessments will no longer be collected.

Given the potential for differential activity of talazoparib and avelumab, as monotherapy and in combination, CCI [redacted] to support the primary endpoint of the study.

Secondary objectives are focused on investigation of candidate biomarkers in tissue (defects in DDR, PD-L1 expression and TMB) and ctDNA (TMB and defects in DDR), that have been shown to have predictive value in identifying those patients who are most likely to benefit from treatment with either anti-PD-L1 or PARP inhibitors.

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Candidate biomarkers to be investigated include, but may not be limited to:

- PD-L1 expression on tumor and infiltrating immune cells measured by immunohistochemistry (IHC).
- The presence/absence of tumor-infiltrating CD8+ T lymphocytes.

7.4.1. Baseline Tumor Tissue Sample (Obsolete)

Baseline tumor tissue sample is no longer applicable as enrollment in this study was stopped on 19 March 2019.

All patients must provide tumor tissue in the form of an FFPE tumor tissue block sufficient to provide a minimum of 25 slides, together with an orginal H&E slide.

If suitable 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. For all biopsies, a core biopsy, using a minimum 18 gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested for each biopsy procedure.

All tumor tissue sections provided should ideally measure 5×5 mm and must contain 40% or greater tumor nuclei per central laboratory assessment.

If a block cannot be provided due to documented local/institutional regulations, sites are requested to provide an original H&E slide and at least 25 unstained slides, each containing a 5-micron tissue section cut serially from the same FFPE block. Positively-charged glass slides should be used, and slides should not be baked.

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.

Sites may randomize/enroll patients who meet all other eligibility criteria while awaiting central confirmation of tissue acceptance, but must provide additional tumor samples in the event that the central lab review shows insufficient sample quality.

Discontinuation of enrollment from sites that consistently fail to submit tissue which is adequate for the planned primary analysis will be at the discretion of the Sponsor.

7.4.2. End of Treatment Tumor Tissue Sample (Obsolete)

Effective with IRB/EC approval of Amendment 2, the end of treatment tumor tissue sample will no longer be collected.

At end of treatment, optional *de novo* (ie, fresh) tumor core biopsies are requested to provide FFPE tumor tissue blocks. If a block cannot be provided due to documented local/institutional regulations, sites are requested to provide at least 15 unstained slides each containing a 5-micron tissue section cut serially from the same FFPE block.

7.4.3. Peripheral Blood Samples (Obsolete)

Effective with IRB/EC approval of Amendment 2, peripheral blood samples will no longer be collected.

As described in the Schedule of Activities tables for all treatment arms, the following blood samples and subsequent analyses will be conducted in order to assess potential biomarkers of response, pharmacodynamic activity and resistance:

- Blood samples (6 mL whole blood) will be collected to assess the frequency and diversity of TCR sequences prior to the start of chemotherapy and maintenance treatments, once during both treatment periods, and at the end of treatment.
- Blood sample (20 mL for processing to plasma) will be collected at screening and prior to the start of chemotherapy and maintenance treatments, once during both treatment periods, and at the end of treatment for processing to circulating tumor DNA (ctDNA) and subsequent analysis of genetic biomarkers that may relate to response and resistance.
- Blood samples (4 mL and 10 mL for processing to plasma and serum, respectively) will be collected prior to the start of chemotherapy and maintenance treatments, C1D15 of maintenance (Arms A and B) and at the end of treatment to assess proteomic, epigenetic and metabolomic factors and signatures.
- Blood samples (2 x 2.5 mL whole blood) will be collected prior to chemotherapy treatment to generate RNA. RNA will be used to assess the level of expression of genes in peripheral blood.
- A single blood sample (4 mL whole blood) will be collected prior to chemotherapy treatment and processed to generate DNA. DNA will be used to assess potential epigenetic or genetic biomarkers that may relate to response to treatment.

7.4.4. Additional Analyses (Obsolete)

Effective with IRB/EC approval of Amendment 2, no additional analyses will be performed.

Analyses in addition to those described above may be warranted based on emerging data. These analyses may include identification or characterization of cells, DNA, RNA, or protein biomarkers. Such biomarkers may aid in the identification of those patients who might preferentially benefit from treatment with the combination of avelumab and talazoparib, may be of relevance to the mechanisms of action of the combination or to the development of resistance to the combination. CCI

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7.5.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, patients will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

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

7.6. Tumor Response Assessments

Effective with IRB/EC approval of Amendment 2, tumor response assessments will be performed per institutional guidelines and at the investigator's discretion. These data will not be recorded in the INFORM database.

Effective with IRB/EC approval of Amendment 2, CA-125 level testing is no longer required per protocol but may be performed as clinically indicated.

The decision for body areas to be scanned will depend on the disease under study and the extent of disease. Tumor assessments must include all known or suspected disease sites. The minimum recommended body areas to be scanned are detailed in the Imaging Manual. All radiographic images will be collected and -will be objectively verified by an independent third party core imaging laboratory as described in Imaging Manual.

Baseline scans must be performed within 28 days prior to randomization.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at screening, at 9 and 18 weeks (±3 days) from the date of randomization and every 12 weeks thereafter until disease progression by BICR assessment per RECIST v1.1, regardless of start of initiation of subsequent anti-cancer therapies. For patients who undergo interval

debulking surgery during chemotherapy period, an additional tumor assessment should be performed after surgery.

In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration or rising CA-125 levels), or when clinically indicated.

The schedule of tumor assessments should be fixed according to the calendar, starting with enrollment/randomization, regardless of treatment schedule or treatment dealy or interuptions due to toxicity.

Imaging may incude chest, abdomen and pelvis CT or magnetic resonance imaging (MRI) scans and other anatomy such as head or neck, as clinically indicated or protocol required. Brain CT or MRI scans are required at baseline for all patients with stable brain lesions and for those for whom central nervous system involvement is suspected. If stable brain metasteses are presnt at baseline, brain imaging should be repeated at each tumor assessment. Otherwise, brain imaging will be conducted post-baseline only when clinically indicated.

Whole body bone imaging using bone scan (bone scintigraphy) or other methods considered standard of care locally such as 18-fluorodeoxyglucose positron emission tomography (^{18}F FDG PET), ^{18}-F-sodium fluoride-PET (^{18}F NaF PET), PET/CT, or MRI is required only if new bone metastases are suspected. Bone lesion(s) identified at baseline by bone scintigraphy, ^{18}F-FDG-PET, ^{18}F-NaF PET, or PET/CT will be further assessed at baseline by correlative imaging, such as diagnostic CT or MRI and subsequently re assessed by diagnostic CT or MRI as per the tumor assessment schedule. Only for those patients with bone lesions present at baseline, whole body bone imaging should be repeated at every other tumor assessment visit and at the time of confirmation of CR. For all patients, whole body bone imaging may be repeated during study as clinically indicated (ie, patient has new or worsening bone pain, increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases).

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

Assessment of response will be made using RECIST version 1.1 (Appendix 3) as assessed by BICR and investigator. Measurable or evaluable lesions that have been previously irradiated will not be considered target lesions unless progression of such lesions has been observed following completion of radiation therapy.

See Section 5.7 for treatment after evidence of disease progression.

CA-125 will be assessed in a local laboratory at screening, on Day 1 of each cycle and at end of treatment. Rising CA-125 levels alone will not be considered evidence of progression.

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

7.7. Patient Reported Outcomes Assessments (Obsolete)

Effective with IRB/EC approval of Amendment 2, patient reported outcome assessments will no longer be collected.

The instruments proposed are the NCCN-FACT FOSI-18 (NFOSI-18) and the EQ-5D-5L to capture disease and treatment-related symptoms and health-related quality of life (HRQoL) as secondary endpoints. The Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C) items will be administered as anchors to establish the meaningful threshold for the disease related symptoms- physical (DRS-P) subscale of the NFOSI-18. CCI [redacted] The PRO instruments selection and administration schedule have been considered with patient burden in mind. All PRO assessments will be administered per the Schedule of Activities tables for each treatment arm.

Once the patient is enrolled in the study, the electronic Patient Reported Outcomes (ePRO) device training should be provided to the patient and the site coordinator should make sure the patient understands the materials and is able to use the device. Patients must complete the questionnaires using the ePRO device at the clinic prior to any study or medical procedure during Day 1 Cycle 1 of chemotherapy period, and take the device home for subsequent assessments.

7.7.1. NFOSI-18 (Obsolete)

Effective with IRB/EC approval of Amendment 2, the NFOSI-18 will no longer be collected.

The NFOSI-18 is an ovarian cancer-specific symptom index comprised of symptoms rated as highest priority by both oncology clinical experts and women with advanced ovarian cancer.[65,66] The NFOSI-18 was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system and was specifically created with the input from the US FDA, including the recommendation that the assessment of specific symptoms is an appropriate starting point for improved measurement of Quality of Life (QoL) domains.[65] It is specifically designed to be a stand-alone instrument to measure disease-related symptoms, treatment side effects and function/well-being in patients with ovarian cancer.

The NFOSI-18 has several subscales. The DRS-P subscale include 9 physical symptoms/concerns (energy, pain, ill, stomach cramps, fatigue, constipation, stomach swelling, bowel control and sleep) and the disease related symptoms-emotional (DRS-E) subscale include 1 emotional symptom/concern (worry condition will get worse). The treatment side effect (TSE) subscale includes 5 items (nausea, hair loss, bothered by side

effects, vomiting and skin problems). The functional well-being (FWB) subscale includes 3 items (able to get around, enjoy life, and content with QoL). As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

The amount of time for a patient to complete the questionnaire is estimated to be about 3 minutes.

7.7.2. PGI-S (Obsolete)

Effective with IRB/EC approval of Amendment 2, the PGI-S will no longer be collected.

The different versions of the Patient Global Impression scale are based on the original Clinical Global Impression scale created by Guy, 1976.[67] The PGI-S is a 1-item questionnaire that can be adapted to assess patient's impression of disease or symptom severity. The PGI-S will be adapted to assess disease-related physical symptoms for this study (See Appendix 5). The severity of the physical symptoms will be assessed on a 5 point Likert scale (eg, 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms, 4=very severe symptoms). The expected questionnaire completion time is less than 1 minute and only to be completed by patients enrolled in the US who are fluent in English.

7.7.3. PGI-C (Obsolete)

Effective with IRB/EC approval of Amendment 2, the PGI-C will no longer be collected.

The PGI-C is a 1 item questionnaire that can be adapted to assess the patient's impression of the change in symptom or overall health status.[67] The PGI-C will be adapted to assess disease-related physical symptoms for this study (See Appendix 5). The change in physical symptoms is assessed on a 7 point Likert scale (eg, -3=very much worse, -2= moderately worse, -1= a little worse, but a meaningful change, 0=about the same, 1=a little better, but a meaningful change, 2=moderately better, 3=very much better). The expected questionnaire completion time is less than 1 minute and only to be completed by patients enrolled in the US who are fluent in English.

7.7.4. EuroQoL EQ-5D-5L (Obsolete)

Effective with IRB/EC approval of Amendment 2, the EQ-5D-5L will no longer be collected.

The EuroQol EQ-5D-5L is a 6 item patient completed questionnaire designed to assess health status in terms of a single index value or utility score.[68,69] 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 based on the health state profile items that allow for imputation of the index score.[69] Overall index scores range from 0 to 1, with low scores representing a higher level of dysfunction.

The amount of time for a patient to complete the questionnaire is estimated to be about 2 minutes.

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8. ADVERSE EVENT REPORTING

8.1. Requirements

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

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

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

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal Section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

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

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

8.1.5. Causality Assessment

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

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

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

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject 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 subject;
- Admission exclusively for the administration of blood products.

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury

(DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4.3.1. Exposure During Pregnancy

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the 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.

8.4.3.2. Exposure During Breastfeeding

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

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

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

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

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

Medication errors include:

- Medication errors involving subject 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 subject.

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

As of 19 March 2019, the Sponsor made the decision to stop enrollment/randomization in study B9991030. Patients who were randomized can continue treatment and will be monitored for appropriate safety assessments until treatment discontinuation. As of 19 March 2019, approximately 11% of the patients originally planned to be randomized in the study had been randomized. Therefore, the study endpoints are no longer applicable and/or feasible. No formal statistical analyses will be conducted, but patient characteristics, duration of treatment and safety data will be summarized by treatment arm.

9.1. Sample Size Determination (Obsolete)

The primary objective of this study is to demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance (Arm A) is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance (Arm C) in prolonging PFS in patients with newly diagnosed advanced ovarian cancer with defects in DNA damage repair (DDR+) (referred to as “DDR+ population” in what follows).

The key secondary objectives of this study are:

- To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance (Arm A) is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance (Arm C) in prolonging OS in patients with newly diagnosed advanced ovarian cancer in the DDR+ population.

- To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance (Arm A) is superior to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance (Arm C) in prolonging PFS in patients with newly diagnosed advanced ovarian cancer unselected for DDR status (all randomized patients).

- To demonstrate that avelumab in combination with platinum-based chemotherapy followed by avelumab plus talazoparib maintenance (Arm A) is superior to platinum-based chemotherapy followed by bevacizumab maintenance (Arm C) in prolonging OS in patients with newly diagnosed advanced ovarian cancer unselected for DDR status (all randomized patients).

The following statistical hypothesis will be tested to address the primary objective:

H_{01}: $HR_{PFS+} \geq 1$ vs. H_{11}: $HR_{PFS+} < 1$.

where HR_{PFS+} is the hazard ratio (Arm A vs. Arm C) of PFS based on BICR assessment in the DDR+ population.

In addition the following statistical hypotheses will be tested to address the key secondary objectives:

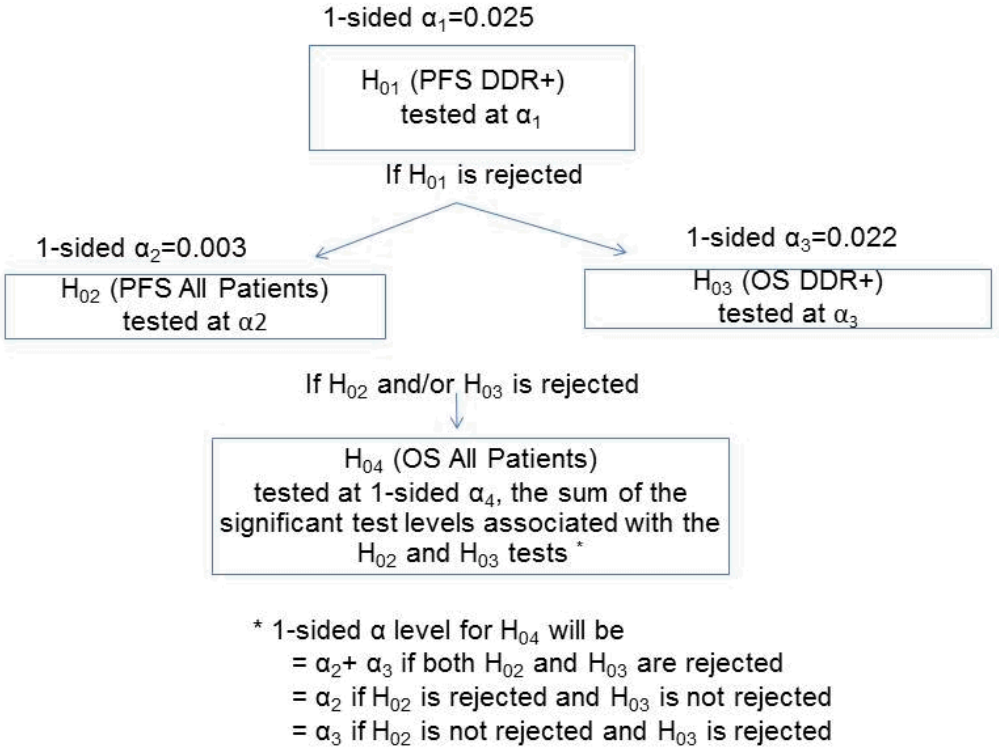
H_{02}: $HR_{PFS} \geq 1$ vs. H_{12}: $HR_{PFS} < 1$;

H_{03}: $HR_{OS+} \geq 1$ vs. H_{13}: $HR_{OS+} < 1$;

H_{04}: $HR_{OS} \geq 1$ vs. H_{14}: $HR_{OS} < 1$.

where HR_{PFS} and HR_{OS} are the hazard ratios (Arm A vs. Arm C) of PFS based on BICR assessment and OS, respectively, in all randomized patients, and HR_{OS+} is the hazard ratio (Arm A vs. Arm C) of OS in the DDR+ population. A gatekeeping procedure as illustrated in Figure 2, will be used to maintain the overall type I-error in the study at or below 1-sided 0.025. The significance levels for each test also take into account the group sequential nature of the design (see Section 9.9).

Figure 2. Statistical Testing Strategy for Arm A vs Arm C Comparisons (Obsolete)



For the primary comparison of PFS between Arm A and Arm C in the DDR+ population, 200 PFS events based on BICR assessment in Arms A and C combined will provide 90% power to detect a HR of 0.63 using a 1-sided log rank test at a significance level of 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 (-9) β-spending function to determine the non-binding futility boundary.

The study will randomize a total of approximately 720 patients in a 2.5:1:2.5 ratio to Arm A (N=300 including N=150 DDR+), Arm B (N=120 including N=60 DDR+), and Arm C (N=300 including N=150 DDR+). Randomization will be stratified by germline BRCA 1/2 mutational status (gBRCA+ vs gBRCA-), and resection status (adjuvant with >1mm and ≤1 cm residual disease vs. adjuvant with residual disease >1 cm vs. neoadjuvant).

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

1. The median PFS for patients in Arm C is 14.1 months,[74] and the median PFS for patients in Arm A is 22.4 months for the DDR+ population and 20.1 months for all randomized patients; this corresponds to a hazard ratio (HR) of 0.63 in the DDR+ population and 0.70 in all randomized patients, respectively under the exponential model assumption;

2. The median OS for patients in Arm C is 39.7 months,[74] and the median OS for patients in Arm A is 56.7 months for the DDR+ population and 52.9 months for all randomized patients; this corresponds to a HR of 0.70 in the DDR+ population and 0.75 in all randomized patients, respectively under the exponential model assumption;

3. PFS drop-out rate of approximately 15% and OS drop-out rate of approximately 5% at the time of primary analysis of PFS and OS, respectively;

4. The DDR+ population includes 50% of the randomized patients;

5. Non-uniform patient accrual accomplished over an 18-month period.

The sample size of approximately 720 patients will also allow an assessment of OS in the DDR+ population, and PFS and OS in all randomized patients.

If H_{01} is rejected then PFS in all randomized patients and OS in the DDR+ population can be tested.

- For the PFS comparison between Arm A and Arm C in all randomized patients, 411 PFS events based on BICR assessment will provide 80.5% power to detect a HR of 0.70 using a 1-sided log-rank test at a significance level of 0.003, and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α -spending function to determine the efficacy boundary.

- For the OS comparison between Arm A and Arm C in the DDR+ population, 207 deaths will provide 70.1% power to detect a HR of 0.70 or 80.1% power to detect a HR of 0.67 using a 1-sided log rank test at a significance level of 0.022, and a 4-look group sequential design with Lan-DeMets (O'Brien-Fleming) α -spending function to determine the efficacy boundary.

If either H_{02} or H_{03} are rejected, then OS in all randomized patients can be tested at the sum of the significance levels associated with the significant H_{02} and H_{03} tests (see Figure 2). With 421 deaths the power to detect a HR of 0.75 is 83.2% (if both H_{02} and H_{03} are rejected), 57.6% (if H_{02} is rejected and H_{03} is not rejected) or 81.9% (if H_{02} is not rejected and H_{03} is rejected) using a 1-sided log rank test at a significance level of 0.025, 0.003 or 0.022, respectively, and a 4-look group sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundary.

The data cut-off for the primary PFS analysis will occur after the target number of PFS events (200) based on BICR assessment in Arms A and C combined in the DDR+ population has been reached and the last patient randomized in the DDR+ population has been followed for at least 12 months after randomization.

The data cut-off for the primary analysis of OS will occur after the target number of deaths (207) in Arms A and C combined in the DDR+ population has been reached.

The study will be considered positive if the 1-sided stratified log-rank test for PFS based on BICR assessment for comparing Arm A to Arm C in the DDR+ population is significant at the pre-specified α level.

To establish that platinum-based chemotherapy followed by talazoparib maintenance (Arm B) has proof of efficacy compared to platinum-based chemotherapy plus bevacizumab followed by bevacizumab maintenance (Arm C), a HR target of 0.792 for Arm B vs. Arm C is deemed to be clinically important (corresponding to a minimum improvement of 3.7 months in median PFS over Arm C under the exponential model assumption). Proof of efficacy for Arm B compared to Arm C will have been demonstrated if both of the following criteria are met in the DDR+ population:

1. Clinical relevance: Estimated $HR_{PFS+ BvsC)} \leq 0.792$.

2. Statistical significance: Probability (true $HR_{PFS+(BvsC)} < 1 \mid$ data) $\geq 80\%$.

where $HR_{PFS+(BvsC)}$ is the HR of Arm B vs. Arm C of PFS based on BICR assessment in the DDR+ population. The calculation of the statistical significance criterion assumes asymptotic normality of log ($HR_{PFS+(BvsC)}$) and a non-informative prior.

Table 13 shows the probability for demonstrating proof of efficacy for Arm B compared to Arm C under different scenarios. If the true $HR_{PFS+(BvsC)}$ is 1 (ie, no difference between the two arms) the probability of claiming proof of efficacy (false detection rate) for Arm B compared to Arm C is 0.099. If the true $HR_{PFS+(BvsC)}$ is 0.68 and the true $HR_{PFS+(AvsC)}$ is 0.63, then 149 PFS events based on BICR assessment would be observed in the DDR+ population for Arms B and C combined at the time of the primary analysis and the probability of declaring proof of efficacy (true detection rate) for Arm B compared to Arm C is 0.80.

Table 13. Operating Characteristics for PFS in the DDR+ Population (Arm B vs. Arm C)—Obsolete

True $HR_{PFS+(BvsC)}$	Probability of demonstrating proof of efficacy*
0.65	0.862
0.68	0.800
0.75	0.618
0.792	0.500
0.90	0.240
1.00	0.099
*Assuming 149 PFS events in the DDR+ population for Arms B and C combined at the time of the primary analysis for PFS.	

9.2. Analysis Populations

Effective with Amendment 2, only the Safety Analysis Set, Pharmacokinetic Analysis Set and Immunogenicity Analysis Set are applicable.

9.2.1. Full Analysis Set (Obsolete)

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 (Obsolete)

The Per Protocol Analysis Set is a subset of the Full Analysis Set and will include patients who receive at least 1 dose of study drug (avelumab, talazoparib, bevacizumab, carboplatin, or paclitaxel) post randomization 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 SAP. The Per-Protocol Analysis Set will be used for sensitivity analyses for the primary efficacy endpoint.

9.2.3. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of study drug (avelumab, talazoparib, bevacizumab, carboplatin, paclitaxel). Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case patients will be classified according to the first treatment received. The safety analysis set will be used for all analyses other than pharmacokinetics or immunogenicity.

9.2.4. Pharmacokinetic Analysis Set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least 1 concentration above the below limit of quantitation (BLQ) of either avelumab or talazoparib.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least 1 of the PK parameters of interest of either avelumab or talazoparib.

9.2.5. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients in Arm A only, who have at least 1 ADA sample collected.

9.2.6. Biomarker Analysis Set (Obsolete)

The biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one baseline biomarker assessment.

CCI [redacted]

9.3. Efficacy Analysis (Obsolete)

Effective with IRB/EC approval of Amendment 2, no efficacy data will be reported in the CSR.

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

All analyses will be performed by using Statistical Analysis System (SAS)® Version 9.1.3 or higher.

All primary and secondary endpoints based on radiological assessments of tumor burden 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 (Obsolete)

The primary endpoint is PFS based on BICR assessment in the DDR+ population.

In what follows, progressive disease (PD) is based on BICR assessment unless otherwise specified.

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

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

A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{01} (Arm A vs Arm C) in the DDR+ population.

The Cox proportional hazards model stratified by randomization stratification factors will be fitted to compute the HR (Arm A vs Arm C, Arm A vs Arm B and Arm B vs Arm C) and the corresponding 95% CIs for PFS in the DDR+ population. In order to account for the group sequential design in this study, the repeated confidence interval (RCI) method[75] will be used to construct the 2-sided RCIs for the HR (Arm A vs. Arm C) at the interim and the final analyses of PFS in the DDR+ population.

If there are large departures from proportional hazards (PH), then PFS by BICR assessment in the DDR+ population will also be analyzed based on restricted mean survival time (RMST) differences.[76]

The RMST is a robust and clinically interpretable summary measure of the survival time distribution. Unlike median survival time, it is estimable even under heavy censoring. There is a considerable body of methodological research[76,77,78] about the use of RMST to estimate treatment effects as an alternative to the hazard ratio approach.

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

The probability of the HR (Arm B vs. Arm C) in the DDR+ population ($HR_{PFS+(BvsC)}$) being less than 1 will be calculated assuming asymptotic normality of $\log(HR_{PFS+(BvsC)})$ a non-informative prior. Proof of efficacy for Arm B compared to Arm C will have been demonstrated if both of the following two criteria are satisfied:

- Clinical relevance: Estimated $HR_{PFS+(BvsC)} \leq 0.792$.
- Statistical significance: Probability (True $HR_{PFS+(BvsC)} < 1 \mid$ data) ≥ 0.80.

In addition, for descriptive purposes, PFS time associated with each treatment arm (Arm A, Arm B, Arm C) will be summarized using the Kaplan-Meier method and displayed graphically where appropriate in the DDR+ population. CIs for the 25th, 50th, and 75th percentiles will be reported.

9.3.2. Analysis of Secondary Endpoints (Obsolete)

9.3.2.1. PFS Based on BICR Assessment in all Randomized Patients (Obsolete)

The methodology described in Section 9.3.1 for PFS based on BICR assessment in the DDR+ population for the Arm A vs Arm C comparison will be followed for PFS based on BICR assessment in all randomized patients. A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{02} (Arm A vs Arm C) in all randomized patients.

In addition, for descriptive purposes, PFS time associated with each treatment arm (Arm A, Arm B, Arm C) will be summarized using the Kaplan-Meier method and displayed graphically where appropriate for all randomized patients. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model stratified by randomization stratification factors will be fitted to compute the HR (Arm A vs Arm C, Arm A vs Arm B and Arm B vs Arm C) and the corresponding 95% CIs for PFS in all randomized patients. In order to account for the group sequential design in this study, the RCI method will be used to construct the 2-sided RCIs for the HR (Arm A vs. Arm C) at the interim and the final analyses of PFS in all randomized patients.

If there are large departures from PH, then PFS by BICR assessment in all randomized patients will also be analyzed based on RMST differences.

9.3.2.2. OS in the DDR+ Population and in all Randomized Patients (Obsolete)

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

A stratified log-rank test (one-sided) stratified by randomization stratification factors will be used at the interim and/or final analyses at the significance level associated with the testing strategy outlined in Section 9.1 for the testing of H_{03} (Arm A vs Arm C) in the DDR+ population and for the testing of H_{04} (Arm A vs Arm C) in all randomized patients.

In addition, for descriptive purposes, OS time associated with each treatment arm (Arm A, Arm B, Arm C) will be summarized using the Kaplan-Meier method and displayed graphically where appropriate in the DDR+ population and in all randomized patients. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model stratified by randomization stratification factors will be fitted to compute the HR (Arm A vs Arm C, Arm A vs Arm B and Arm B vs Arm C) and the corresponding 95% CIs for OS in the DDR+ population and in all randomized patients. In order to account for the group sequential design in this study, the RCI method will be used to construct the 2-sided RCIs for the HR (Arm A vs. Arm C) at the interim and the final analyses of OS in the DDR+ population and in all randomized patients.

If there are large departures from PH, then OS in the DDR+ population and in all randomized patients will also be analyzed based on RMST differences.

9.3.2.3. PFS Based on Investigator Assessment (Obsolete)

Using investigator's assessment, PFS time associated with each treatment arm (Arm A, Arm B, Arm C) will also be summarized using the Kaplan-Meier method and displayed graphically where appropriate in the DDR+ population and in all randomized patients. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model stratified by randomization stratification factors will be fitted to compute the HR (Arm A vs Arm C, Arm A vs Arm B and Arm B vs Arm C) and the corresponding 95% CIs for PFS in the DDR+ population and in all randomized patients.

9.3.2.4. PFS on Next-line Therapy (PFS2) Based on Investigator Assessment (Obsolete)

PFS2 is defined as time from randomization to the start of second subsequent treatment after first disease 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 in the DDR+ population and in all randomized patients will be summarized by treatment arm using Kaplan-Meier methodology and displayed graphically, where appropriate. The median PFS2 and 95% CI for the median will be provided for each treatment arm.

9.3.2.5. PFS per GCIG Criteria Based on Investigator Assessment (Obsolete)

PFS based on investigator assessment per GCIG criteria will be assessed incorporating both RECIST 1.1 and CA-125 (Appendix 4).

PFS based on investigator assessment per 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 based on investigator assessment per GCIG criteria in the DDR+ population and in all randomized patients 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.

9.4. Pharmacokinetic Analysis

The results of the pharmacokinetic analyses on samples collected prior to IRB/EC approval of protocol amendment 2 will not be included in the CSR but will be retained by the Sponsor and may be pooled with data from other studies to further inform the development programs of avelumab and talazoparib, as appropriate.

Pharmacokinetic data analyses will include pre-dose and post-dose sampling for serum avelumab and predose plasma talazoparib as per the Schedule of Activities. PK data analyses will include descriptive summary statistics of the pre dose/trough (C_{trough}) concentrations for both investigational products and maximum (C_{max}) concentrations (for avelumab) for each cycle.

9.4.1. PK Analysis for Avelumab and Talazoparib

Effective with IRB/EC approval of Amendment 2, the PK analysis for avelumab and talazoparib will be limited to samples collected.

Avelumab and talazoparib concentrations will be summarized descriptively (n, mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean and its associated CV) by Dose (talazoparib only), cycle, day and nominal time. Individual patient and median profiles of the concentration time data will be plotted by dose, cycle and day using nominal times. Individual and median profiles will be presented on both linear-linear and log-linear scales.

9.4.2. Population Pharmacokinetic and Exposure Response Analysis

Effective with IRB/EC approval of Amendment 2, no population PK and exposure response analysis will be performed on data from this study; however PK data may be pooled with data from other studies to further inform the development programs of avelumab and talazoparib, as appropriate.

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

9.4.3. Analysis of Immunogenicity Data of Avelumab

Immunogenicity analysis will be limited to samples collected prior to IRB/EC approval of amendment 2 and will be perfomed as appropriate.

ADA/NAb data will be listed and summarized for each dosing interval for avelumab.

The percentage of patients with positive ADA and neutralizing antibodies each will be summarized 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. The effect of ADA on avelumab concentrations will be evaluated.

9.5. Biomarker Analysis for Secondary CCI [redacted] Endpoints (Obsolete)

Effective with IRB/EC approval of Amendment 2, no biomarker data will be reported in the CSR.

All analyses of biomarkers will be performed based on the biomarker analysis set.

Biomarker data will include baseline, on treatment and end of treatment measurements of biomarkers as detailed in Section 7.4.

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

Appropriate change from baseline measurements will be provided. For discrete measurement biomarkers, frequencies and percentages of categorical biomarker measures will be provided for baseline and on treatment/post treatment time points, as appropriate; shift tables may also be provided.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Fisher's exact test, Wilcoxon signed rank test, Wilcoxon rank sum test, correlation/linear regression, Kaplan-Meier estimate, etc, as appropriate. The statistical approaches will examine correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as progression free survival.

9.6. Analysis of Patient Reported Outcomes (Obsolete)

Effective with IRB/EC approval of Amendment 2, no PRO data will be reported in the CSR.

The FAS will be used for the NFOSI-18 and EQ-5D-5L analyses. The PRO analysis below will be conducted in the DDR+ subset and also in all randomized patients.

The NFOSI-18 and EQ-5D-5L will be scored according to their respective scoring or user guides.[79] For the EQ-5D-5L, the index scores will be calculated using the published weights (tariffs) for the United Kingdom. Specific country weights may be applied for country specific analyses as needed.

The primary PRO analysis will include treatment comparison of Arm A vs. Arm C on the time to deterioration (TTD) of the DRS-P in the DDR+ population. TTD is defined as the time from randomization to deterioration where deterioration is defined, respectively, as a ≥3-point decrease, maintained for 2 consecutive assessments, on the DRS-P (9 items) for physical symptoms or concerns of disease.

The TTD cut-off point proposed above for DRS-P is based on the clinically important differences calculation given by Yost and Eton[80] as a general guidance for the FACIT measurement system. The TTD for DRS-P will be calculated as of the date of randomization and to the date of the first of the 2 consecutive assessments used to identify the event. A decline in DRS-P score represents an increase in physical symptoms or concerns of the disease. Patients who do not have a TTD event will be censored on the date when they last completed a PRO assessment. TTD will be compared between treatment arms using a one-sided log-rank test stratified by randomization stratification factors. No adjustment for multiplicity will be conducted. The Cox proportional hazards model stratified by the randomization factors and will be fitted to compute the hazard ratio (HR) and corresponding 95% CIs. Kaplan-Meier estimates will be presented by treatment arm together with a summary of associated statistics including the median TTD time with 2-sided 95% CIs. The TTD cut-off for the DRS-P will be also examined using an anchor-based method with the PGI-S and PGI-C items and the cumulative distribution function.[81]

Additionally, summary statistics (mean and standard deviation [SD], median, range) of absolute scores over time will be reported for each of the total and subscales of the NFOSI-18, EQ-5D-5L index, and EQ-VAS. The mean change of absolute scores from baseline (and 95% CI) over time will also be reported. Line charts depicting the means and changes from baseline with with standard error (SE) over time will be provided for each treatment arm. For the EQ-5D-5L health state profiles, the proportions of patients reporting having "none", "slight", "moderate", "severe", or "extreme/unable" problems at each time point will be reported.

Several secondary PRO analyses will be conducted. The NFOSI-18 total scores, subscales, a single question within the TSE subscale ("I am bothered by side effects of treatment"), as well as the EQ-5D-5L index and VAS scores will be assessed for the comparisons among treatment arms using a mixed effects logitudinal model. The main analysis will be applied using scheduled assessments from baseline up to EOT (not including EOT), and the secondary analysis will be based on all scheduled assessments from baseline including EOT and until 3 years from patient's enrollment.

Time from randomization to development of significant side effect bother (TTB) will be analyzed similarly to the analysis of TTD of DRS-P 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 NFOSI-18 assessment if they have not had a TTB event. This analysis will be applied using scheduled assessments from baseline up to EOT (not including EOT) to assess the level of treatment side effect bother on patients during the treatment period, and also using all scheduled assessments from baseline including EOT and until 3 years from patient' enrollment to also assess the level of treatment side effect bother on patients from the next line of therapy. TTB will be compared between treatments using a one-sided log-rank test stratified by randomization stratification factors. No adjustment for multiplicity will be conducted. The treatment effect will be estimated using a Cox proportional hazards model stratified by the randomization factors and fitted to compute the hazard ratio (HR) and corresponding 95% CIs. Kaplan-Meier estimates will be presented by treatment arm together with a summary of associated statistics including the median TTB time with 2-sided 95% CIs.

CCI [redacted]

CCI [redacted]

[redacted]

CCI

CCI

9.8. Safety Analysis

Descriptive statistics will be used to summarize all patient characteristics, duration of treatment , and AEs/SAEs. Data will also be displayed graphically, where appropriate.

9.8.1. 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 Grade.

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 or higher, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for AEs of clinical interest may be further assessed as described in the SAP.

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

9.8.2. Laboratory Abnormalities (Obsolete)

Effective with IRB/EC approval of Amendment 2, no summary of laboratory data will be reported in the CSR. Only listings of laboratory test data will be provided

The laboratory 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.

9.8.3. Electrocardiograms (Obsolete)

Effective with IRB/EC approval of Amendment 2, no electrocardiograms data will be reported in the CSR.

ECG measurements and changes from baseline will be summarized by treatment arm and visit. Interval measurements from clinically indicated on treatment 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.

9.9. Interim Analysis (Obsolete)

Effective with IRB/EC approval of Amendment 2, interim analysis is no longer applicable.

The interim and the primary analyses for each efficacy endpoint will be performed after all patients have been randomized in the study and the target number of events has occurred in Arms A and C combined as described below. A maximum of 4 distinct analyses cut-offs are planned in the study at the approximate calendar times described below:

- At the time when 140 PFS events (70% of the expected 200 events) based on BICR assessment have occurred in the DDR+ population in Arms A and C combined;
- At the time when 200 PFS events based on BICR assessment have occurred in the DDR+ population in Arms A and C combined;
- At the time when 155 deaths (74.9% of the expected 207 deaths) have occurred in the DDR+ population in Arms A and C combined;
- At the time when 207 deaths have occurred in the DDR+ population in Arms A and C combined.

Table 14 displays the maximum number of analyses expected for the primary endpoint and the associated efficacy and futility boundaries. The futility boundaries are non-binding but the study may be stopped for futility if at the time of the interim analysis the futility boundary is crossed. If the efficacy boundary is crossed at the time of the interim analysis or at the time of the primary analysis then the primary objective of the study will have been demonstrated.

Table 14. PFS Based on BICR Assessment in the DDR+ Population (Arm A vs. Arm C) - Efficacy and Futility Boundaries (Obsolete)

	PFS in the DDR+ Population	
Analysis	**IA1**	**PA**
Analysis cut-off trigger	140 PFS events in DDR+	200 PFS events in DDR+
Number of events[a] (Information fraction)	140 (70.0%)	200 (100%)
p-value (z-value) for efficacy	<0.0074 (<-2.438)	<0.0228 (<-2.000)
p-value (z-value) for futility[b]	>0.3975 (>-0.260)	NA

[a] Number of events expected under H_{11} for PFS (assuming a HR of 0.63).
[b] Non-binding.
IA1=interim analysis 1, PA=primary analysis

Table 15 displays the analysis triggers for PFS in all randomized patients and the analysis triggers for OS in the DDR+ population, as well as the associated efficacy boundaries. As described in Section 9.1, the significance level for the analyses of these endpoints is determined by the gatekeeping procedure.

Table 15. PFS Based on BICR Assessment in All Randomized Patients and OS in the DDR+ Population (Arm A vs. Arm C) - Efficacy Boundaries (Obsolete)

	Endpoints					
	PFS in all randomized patients		OS in the DDR+ Population			
Analysis	**IA1**	**PA**	**IA1**	**IA2**	**IA3**	**PA**
Analysis cut-off trigger	140 PFS events in DDR+	200 PFS events in DDR+	140 PFS events in DDR+	200 PFS events in DDR+	155 deaths in DDR+	207 deaths in DDR+
Number of events[a] (Information fraction)	289 (70.3%)	411 (100%)	66 (31.9%)	110 (53.1%)	155 (74.9%)	207 (100%)
p-value (z-value) for efficacy	<0.0004 (<-3.352)	<0.0029 (<-2.762)	<0.00005 (<-3.891)	<0.0017 (<-2.936)	<0.0076 (<-2.428)	<0.0194 (<-2.065)

[a] Number of events expected under H_{12} for PFS (assuming a HR of 0.70) and H_{13} for OS (assuming a HR of 0.70).
IA1=interim analysis 1, IA2=interim analysis 2, IA3=interim analysis 3, PA=primary analysis

Table 16 displays the analysis triggers for OS in all randomized patients, as well as the associated efficacy boundaries. As described in Section 9.1, the significance level for the analyses of this endpoint is determined by the gatekeeping procedure.

Table 16. OS in All Randomized Patients (Arm A vs. Arm C) – Efficacy Boundaries (Obsolete)

	OS in All Randomized Patients			
Analysis	**IA1**	**IA2**	**IA3**	**PA**
Analysis cut-off trigger	140 PFS events in DDR+	200 PFS events in DDR+	155 deaths in DDR+	207 deaths in DDR+
Number of events[a] (Information fraction)	135 (32.1%)	225 (53.4%)	317 (75.3%)	421 (100%)
p-value (z-value) for efficacy[b]	<0.00008 (<-3.789)	<0.0021 (<-2.856)	<0.0091 (<-2.361)	<0.0219 (<-2.016)

[a] Number of events expected under H_{14} for OS (assuming a HR of 0.75).
[b] The p-values and z-values noted for OS are those associated with the scenario when both H_{02} and H_{03} are rejected.
IA1 = interim analysis 1, IA2 = interim analysis 2, IA3=interim analysis 3, PA = primary analysis

Since the observed number of events at the interim analysis may not be exactly equal to the planned number of events, the efficacy and futility boundaries will be updated based on the actual number of observed events using the pre-specified α-and β-spending functions. Therefore, the observed Z-test statistic at the interim analysis will be compared with the updated efficacy and futility boundaries. If the study continues to final analysis, the p-value that will be used to declare statistical significance at the final analysis for each endpoint will be based on the actual number of events documented at the cut-off date for the final analysis and the α already spent at the interim analysis.

9.10. Data Monitoring Committee (Obsolete)

As of 19 March 2019, the initial E-DMC meeting had not yet occurred. This study will no longer use an external data monitoring committee (E-DMC).

The E-DMC planned an initial review of safety data without holding of recruitment, after approximately 30 patients in the study (approximately 12 patients to the avelumab plus talazoparib combination, Arm A) have been treated and followed for at least 4 weeks after the first dose in the maintenance period. The E-DMC assessment will be conducted based on the available safety data and on all the available safety data of other patients treated up to that data cut-off.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. 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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (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. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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 subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal, and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific numerical code based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, 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 the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study patient or her legally acceptable representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's legally acceptable representative, the subject'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 subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the subject'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 subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 All Participating Countries

End of trial in all 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 or talazoparib at any time.

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

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the 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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

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

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

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

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
ACTH	Adrenocorticotopic Hormone
ADA	Anti-Drug Antibody
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
ADR	adverse drug reactions
AESI	AE of special interest
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ANC	Absolute neutrophil count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
aPPT	activated partial thromboplastin time
ATM	ataxia telangiectasia mutated
AUC	area under the concentration (for carboplatin dosing)
AUC	area under the curve
BBS	Biospecimen Banking System
BCCL	baseline creatinine clearance
BCRP	breat cancer resistance protein
BICR	Blinded Independent Central Review
BLQ	below limit of quantitation
BOR	best overall response
BP	blood pressure
BRCA	BReast CAncer Gene
CAG	clinical assay group (Pfizer)
CEA	carcinoembryonic antigen
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CL_{CR}	creatinine clearance
CL/F	oral clearance
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRPC	castration-resistant prostate cancer
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Clinical trial

Abbreviation	Term
CT	computed tomography
CTA	clinical trial application
CTLA4	cytotoxic T-lymphocyte-associated antigen 4
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	coefficient of variation
CYP450	cytochrome P450
DCIS	ductal carcinoma *in situ*
DDI	drug-drug interaction
DDR	DNA damage repair
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRS-E	disease related symptoms-emotional
DRS-P	disease related symptoms- physical
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organization for Research and Treatment of Cancer
EOT	end of treatment
EPO	erythropoietin
ePRO	electronic patient reported outcomes
ESMO	European Society for Medical Oncology
EQ-5D-5L	EuroQol EQ-5D-5L
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	The Food and Drug Administration
^{18}F FDG PET	18-fluorodeoxyglucose positron emission tomography
FFPE	formalin fixed, paraffin embedded
FIGO	International Federation of Gynecology and Obstetrics
^{18}F NaF PET	^{18}-F-sodium fluoride-PET
FSH	follicle-stimulating hormone
FTC	fallopian tube cancer
FWB	functional well-being

Abbreviation	Term
gBRCA	germline BReast CAncer Gene
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GVHD	graft versus host disease
GOG	Gynecologic Oncology Group
H&E	Hemotoxylin and Eosin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICD	Informed consent document
ICH	International Conference on Harmonisation
ICON	International Collaboration on Ovarian Neoplasms
ICOSL	inducible costimulator ligand
ID	identification
IDS	interval debulking surgery
IFN-α	interferon alpha
IgG1	immunoglobulin G1
IL	interleukin
IND	investigational new drug application
IHC	immunohistochemistry
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
irAE	immune-related adverse event
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IV	intravenously
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LCIS	lobular carcinoma *in situ*
LFT	liver function test
LOH	loss of heterozygosity
LPLV	last patient last visit

Abbreviation	Term
mAb	monoclonal antibody
MCC	Merkel cell carcinoma
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
mPFS	median progression free survival
MRI	magnetic resonance imaging
mTPI	modified toxicity probability interval
N/A	not applicable
NAb	neutralizing antibody
NCI	National Cancer Institute
NCT	National Clinical Trial
NE	Not evaluable
NEMO	NF-κB essential modulator
NFOSI-18	NCCN-FACT FOSI-18
NK	natural killer
NKG2DL	natural killer group 2 member D Ligand
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PARP	Poly (adenosine diphosphate [ADP]-Ribose) Polymerase
PBMC	peripheral blood mononuclear cells
PCD	primary completion date
PCT	physician-choice therapies
PD	pharmacodynamics
PD	progression of disease
PD-1	programmed death–1
PD-L1	programmed death ligand 1
PDS	primary debulking surgery
PET	positron emission tomography
PFS	Progression free survival
PGI-S	Patient Global Impression scale
PGI-C	Patient Global Impression change
PH	proportional hazards
PI	principal investigator
PK	pharmacokinetic
PLD	pegylated liposomal doxorubicin
PPC	primary peritoneal cancer
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
PTEN	phosphatase and tensin homolog gene
Q2W	every 2 weeks

Abbreviation	Term
Q3W	every 3 weeks
QD	every day
QoL	Quality of Life
QW	every week
RCC	Renal cell carcinoma
RCI	repeated confidence interval
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCCHN	squamous cell cancer of the head and neck
SCLC	small cell lung cancer
SE	standard error
SOA	schedule of activities
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SRSD	single reference safety document
SST	serum separator tube
STING	stimulator of interferon genes
TBili	total bilirubin
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TKI	Tyrosine kinase inhibitors
TMB	tumor mutational burden
TNM	Classification of Malignant Tumours
TO	target occupancy
TSE	treatment side effect
TTB	Time to development of significant side effect bother
TTD	time to deterioration
UC	urothelial carcinoma
UICC	Union for International Cancer Control
ULN	upper limit of normal
US	United States
US FDA	United States Food and Drug Administration
V/F	volume of distribution
VAS	Visual Analogue Scale
VEGF	vascular endothelial growth factor
WBC	White blood cell
WHO	World Health Organization
WRD	Worldwide Research and Development
WT	wild type

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

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

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.[82]

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.

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

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to 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 the lesion is considered to have disappeared, 0 mm should be recorded; otherwise if a lesion is determined to be present but too small to measure, the lesion status will indicate "too small to measure and judged to be less than 10 mm" and 5 mm will be used in the calculation of the sum of the diameters.

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

Non target disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, (smallest sum of diameters considers baseline and all assessments prior to the time point under evaluation) but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- 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.

- Not evaluable (NE): 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, or
  - One or more non-target lesions cannot be assessed (eg, poorly visible or unclear images), or
  - One or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

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

Supplemental Investigations

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

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.

Determination of Tumor Response by RECIST

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

Objective Response Status at each 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

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

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

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

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

Objective Response Status at each Evaluation for Patients with Non-Target Disease Only

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

Determination of Best Overall Response

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

Appendix 4. PFS by GCIG Criteria (Obsolete)

As described in published guidelines,[88] 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.

Appendix 5. Patient Global Impression of Severity (PGI-S) (Obsolete)

Patient Global Impression of Severity (PGI-S)

Please choose the response below that best describes the severity of the physical symptoms you experienced from ovarian cancer in the past week.

no symptoms

mild symptoms

moderate symptoms

severe symptoms

very severe symptoms

Patient Global Impression of Change (PGI-C)

Please choose the response below that best describes the overall change from the start of the study in the physical symptoms you experience from ovarian cancer.

very much better

moderately better

a little better, but a meaningful change

about the same

a little worse, but a meaningful change

moderately worse

very much worse

Appendix 6. Revised Schedule of Activities – Effective with Amendment 2

The revised SOA below will be followed in place of the SOA in the Protocol Summary Section of the protocol. The SOA provides an overview of the protocol visits and procedures for each treatment arm. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

Table 1.0. Schedule of Activities: Chemotherapy + Avelumab Followed by Avelumab + Talazoparib (Arm A)/Chemotherapy Followed by Talazoparib Alone (Arm B)

Protocol Activities	On -Treatment				Post Treatment Period	
	Chemotherapy Period (1 cycle = 3 weeks = 21 days)	Maintenance Period (1 cycle = 6 weeks = 42 days)				
	Day 1 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	End of Treatment/Withdrawal[12]	Short-Term Follow-up (Day 30, 60, and 90 ±3 days)[13]
Required Clinical Assessments						
Blood Pressure, Temperature, Pulse[1]	X	X	X	X	X	
Contraception Check[2]	X	X		X	X	X
Hematology, Blood chemistry[3]	X	X	X	X	X	X (Day 30)
Serum/Urine Pregnancy Test[4]	X	X		X	X	
Thyroid Function/ACTH	C2D1, C4D1, and C6D1 only	C1D1, then every 12 weeks thereafter			X	
Paclitaxel/Carboplatin Administration[5]	X					
Avelumab Administration[6]	X (Arm A only)	X (Arm A only)	X (Arm A only)	X (Arm A only)		
Talazoparib[7]		Once daily				
Serious and Non-Serious Adverse Event Monitoring[9]	Monitored and recorded throughout treatment				X	X
Concomitant Treatment(s)[10]	Recorded subject's source document's.				X	X
Urinalysis	Not required per protocol, but may be performed as clinically indicated					
CA-125	Not required per protocol, but may be performed as clinically indicated					
Physical examination	Not required per protocol, but may be performed as clinically indicated					
ECOG Performance Status	Not required per protocol, but may be performed as clinically indicated					
12-Lead Electrocardiogram (ECG)	Not required per protocol, but may be performed as clinically indicated					
Tumor Assessments (including scans)[11]	Performed per institutional guidelines and at investigator's discretion.					

Table 2.0 Schedule of Activities: Chemotherapy + Bevacizumab Followed by Bevacizumab (Arm C)

Protocol Activities	On -Treatment			Post Treatment Period	
	Chemotherapy Period (1 cycle = 3 weeks = 21 days)	Maintenance Period (1 cycle = 6 weeks = 42 days)			
	Day 1 (±3 days)	Day 1 (±3 days)	Day 22 (±3 days)	End of Treatment/Withdrawal[12]	Short-Term Follow-up (Day 30, 60, and 90 ±3 days)[13]
Clinical Assessments (Required)					
Blood Pressure, Temperature, Pulse[1]	X	X	X	X	
Contraception Check[2]	X	X	X	X	X
Hematology, Blood chemistry[3]	X	X	X	X	X (Day 30)
Serum/Urine Pregnancy Test[4]	X	X	X	X	
Thyroid Function/ACTH	C2D1, C4D1, and C6D1 only	C1D1, then every 12 weeks thereafter		X	
Paclitaxel/Carboplatin Administration[5]	X				
Bevacizumab Administration[8]	X	X	X		
Serious and non-serious adverse event monitoring[9]	Monitored and recorded throughout treatment			X	X
Concomitant Treatment(s)[10]	Recorded in subject's source document's			X	X
Urinalysis	X	X	X	X	
CA-125	Not required per protocol, but may be performed as clinically indicated				
Physical examination	Not required per protocol, but may be performed as clinically indicated				
ECOG Performance Status	Not required per protocol, but may be performed as clinically indicated				
12-Lead Electrocardiogram (ECG)	Not required per protocol, but may be performed as clinically indicated				
Tumor Assessments (including scans)[11]	Performed per institutional guidelines and at investigator's discretion.				

Footnotes for Schedule of Activities Tables

1. Blood Pressure, Temperature, Pulse: Effective with Amendment 2, vital signs including weight, height, blood pressure, temperature, and pulse rate are to be performed per SOA above. These data do not need to be recorded in the INFORM database, unless the findings support an AE/SAE.
2. Contraception Check: Only for patients who are of child-bearing potential.
3. Hematology, and Blood Chemistry: Hematology and Blood Chemistry must be collected at Day 1 of each chemotherapy Cycle (unless done in the prior 3 days), and on Day 1, Day 15 and Day 29 of each maintenance cycle, and End of Treatment/Withdrawal and at Day 30 during the follow-up in Arms A/B. Hematology and Blood Chemistry must be performed at Day 1 of each chemotherapy cycle, and on Days 1, and 22 of each maintenance cycle, and end of treatment/withdrawal and at Day 30 during the follow-up in Arm C. Any test may also be performed when clinically indicated.

4. Serum/Urine Pregnancy Test: For women of childbearing potential, a serum or urine pregnancy test must be performed on Day 1 of each chemotherapy cycle, on Day 1 and Day 29 (Arms A and B) and Day 1 and Day 22 (Arm C) of each maintenance cycle, and at the end of study treatment. The pregnancy test should be repeated if 1 menstrual cycle is missed or if the potential of pregnancy is otherwise suspected.
5. Paclitaxel/Carboplatin Administration: Paclitaxel 175 mg/m2 IV, followed by carboplatin dose AUC 5 or AUC 6 IV on Day 1 of every chemotherapy cycle as described in Section 5.4. Premedication will be administered as specified in Section 5.4.1.1. On visits when chemotherapy is administered in combination with avelumab or bevacizumab (Day 1 of each 21-day cycle), chemotherapy will be infused before either avelumab or bevacizumab. See Section 5.4.2 and Section 5.4.3. See Section 6.2 for guidance on treatment duration
6. Study Treatment Avelumab (Arm A Only): Patients will receive avelumab 800 mg administered on Day 1 of each 3-week cycle intravenously after administration of paclitaxel and carboplatin during the chemotherapy period. During the maintenance period patients will receive avelumab 800 mg administered once every 2 weeks after dosing with talazoparib on Days 1, 15, and 29 of each 6-week maintenance cycle. See Section 6.2 for guidance on treatment duration.
7. Study Treatment Talazoparib (Arms A and B, Maintenance Period Only): Talazoparib will be self-administered orally once per day at 0.75mg and will continue through end of Maintenance treatment. On Days 1, 15, and 29 of each Maintenance cycle, the daily dose of talazoparib should not be taken prior to the study visit and will be taken at the clinic after all procedures/assessments have been completed and for patients randomized to Arm A, before the avelumab infusion. See Section 6.2 for guidance on treatment duration.
8. Study Treatment Bevacizumab (Arm C Only): Patients will receive bevacizumab 15mg/kg administered once every 3 weeks intravenously on Day 1 of Cycle 2, 3, 4, 5, and 6 of chemotherapy (may begin with cycle 1 if surgery completed >4 weeks prior to randomization and no contraindications) for adjuvant patients, and on Day 1 of Cycles 1, 2, 5, and 6 for neoadjuvant patients. During Maintenance, bevacizumab will be administered once every 3 weeks intravenously on Days 1 and 22 of each cycle. See Section 6.2 for guidance on treatment duration.
9. Adverse Events: Adverse events (AE) should be documented and recorded at each visit using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.
10. Concomitant Medications/Treatments: Concomitant medications and treatments will be recorded in the patient's source document. However, these do not need to be captured in the INFORM database unless they contribute or are associated with the treatment for an AE.
11. Tumor Assessments: Tumor response assessments will be performed per institutional guidelines and investigator's discretion.
12. End of Treatment/Withdrawal: Performed when criteria for treatment discontinuation are met. Obtain these assessments if not completed within the prior week.
13. Short-Term Follow-up: All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment.