A PHASE 2 STUDY TO EVALUATE SAFETY AND ANTI-TUMOR ACTIVITY OF AVELUMAB IN COMBINATION WITH TALAZOPARIB IN PATIENTS WITH BRCA OR ATM MUTANT TUMORS

JAVELIN BRCA/ATM

Investigational Product Number:	MSB0010718C MDV3800, BMN 673
Investigational Product Name:	Avelumab (MSB0010718C) Talazoparib (MDV3800, BMN 673)
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trials Database (EudraCT) Number:	2018-000345-39
ClinicalTrials.gov Registry Number:	NCT03565991
Protocol Number:	B9991032
Phase:	2b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original Protocol	15 March 2018	Not applicable (N/A)
Protocol Amendment 1	15 November 2018	1. Based on limitations in utility of this and/or complexity to collect this exploratory endpoint, irRECIST assessments and any associated elements were removed or revised accordingly (Protocol Summary; Schedule of Assessments; Section 2; Section 5.4.7; Section 7.6; Section 16; Appendix 4 (removed). 2. To help facilitate study conduct, the Schedule of Activities has been modified with a -1 day window for the baseline physical examination and a +/-3 day window (formerly +/- 2 day) for treatment visits. 3. To help facilitate study conduct, the Schedule of Activities and Section 7.8 has been modified to clarify that Patient Reported Outcome assessments are not required when not available in a language understood by the patient, and to provide a window for shipment of pre-treatment tumor tissue. 4. The background section has been updated with health authority approvals for Avelumab (Section 1.1.1) and Talazoparib (Section 1.1.2). 5. Consistent with the updated Avelumab Investigator's Brochure (version 8, 16 May 2018), the protocol was revised to update background information and recommendation for management of Grade 1 to 2 immune-related rash was updated (Section 5.4.6.5).

Document	Version Date	Summary of Changes and Rationale
		6. Consistent with the updated Talazoparib Investigator's Brochure (dated August 2018), the protocol was revised to provide updated background information on clinical experience (Section 1.2.2.1) and pharmacokinetic information (Section 1.2.2.3), to increase the duration of contraception use (Exclusion criterion #24, Section 4.1; Section 4.3), and to simplify language regarding prohibited medication P-gp inhibitors (Exclusion criterion #19 and Section 5.7.10). 7. Preliminary safety information and the recommended phase 2 dose from the B9991025 study has been added to the Background (Sections 1.2.5.2 and 1.2.6), Allocation to Treatment (Section 5.1) and Talazoparib administration sections (Section 5.4.2 and 5.4.6.2). 8. Use of a Patient Enrollment Verification Form has been added to Section 4.0. 9. To facilitate participation by sites, requirements for specific laboratories for local germline testing has been simplified to be less restrictive: The presence of gene defects must have been determined by local assessment and classification using a test of either germline or tumor DNA, which was performed in a CAP/CLIA certified (or comparable local or regional certification) laboratory (Section 4.1). 10. For increased consistency across tumor types, Inclusion criteria details for platinum sensitivity in breast cancer (Criterion #2.b) 'any other advanced solid tumor' (Criterion #2.e) have been

Document	Version Date	Summary of Changes and Rationale
		modified to 'patients must not have had disease progression within 6 months of initiation of a platinum-containing regimen in Section 4.1. 11. Talazoparib starting dose for patients with renal impairment has been clarified in 5.4.2 and for consistency with other studies, dose modifications due to renal impairment during the study based on creatinine clearance have been removed from Sections 5.4.2, 5.4.6.2 and from Table 5. 12. Permissible highly effective methods of contraception were updated as per current protocol standard, including the addition of sexual abstinence (Exclusion criterion #24; Section 4.3). 13. Definition of menopausal state has been revised as per current standard (Inclusion criterion #11; Section 4.3). 14. Compliance definitions have been added for avelumab (Section 5.2.1) and Talazoparib (Section 5.2.2) and instructions on missed Talazoparib dosing have been added to Section 5.4.2. 15. As separate withdrawal of consent form is not applicable to this study, reference to this was removed from Section 6.3.1. 16. Pregnancy testing language has been simplified and aligned with current standards in Section 7.1.1. 17. Required safety laboratory tests (Table 8, Section 7.1.4) were updated as follows: • As many centers perform an activated partial thromboplastin time assessment (aPTT) rather than

Document	Version Date	Summary of Changes and Rationale
		PTT, aPTT was added as an alternate coagulation test. • Given potential variation in reporting of PT results across study centers, PT has been removed as a reportable test result in favor of collecting the INR result alone (Table 8, Section 7.1.4). 18. More detailed language regarding the informed consent process, from the new protocol template has been incorporated into Section 12.3. Related editorial updates have been made for consistency and readability.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Mechanism of Action/Indication

Avelumab is a human immunoglobulin (Ig)G1 monoclonal antibody (mAb) directed against programmed death-ligand 1 (PD-L1). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint pathway.

In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first treatment for metastatic Merkel cell carcinoma (mMCC), with subsequent approvals in the European Union (EU), Switzerland, Japan, Australia, Israel and Canada. In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[5] Avelumab is currently being investigated as a single agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies.

Talazoparib is a potent, orally bioavailable poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, which is cytotoxic to human cancer cell lines harboring gene mutations that compromise deoxyribonucleic acid (DNA) repair, an effect referred to as synthetic lethality, and by trapping PARP protein on DNA, thereby preventing DNA repair, replication, and transcription.

The combination of avelumab and talazoparib is expected to produce additive or synergistic anti-tumor activity relative to each drug used as a single agent. Avelumab in combination with talazoparib will be investigated in patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or loss-of-function somatic BReast CAncer susceptibility gene (BRCA)1, or BRCA2, or ataxia telangiectasia mutated (ATM) gene defect, as determined by local assessment and classification, who have received at least 1 line of standard of care (SOC) treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified.

Background

Avelumab, as a single agent, has demonstrated efficacy in patients across different tumor types, including previously untreated and treated non-small cell lung cancer (NSCLC), urothelial cancer, ovarian cancer, breast cancer, mMCC, gastric/gastroesophageal junction cancer (GC/GEJ) and castration-resistant prostate cancer (mCRPC). The efficacy findings for avelumab are summarized in the table below.

Avelumab: Efficacy Results

Study	Tumor Type (n)	Efficacy Results
EMR100070-003 (JAVELIN Merkel 200)	**mMCC**[5] 2L, pretreated, metastatic (88)	ORR:[a] 33.0% (n=29, 95% CI: 23.3, 43.8) DOR range, mo: 2.8, 23.3+
EMR100070-001	**Urothelial Carcinoma**[5] Pretreated, advanced or metastatic (161, with ≥6 mo follow-up)	ORR:[a] 16.1% (n=26, 95% CI: 10.8, 22.8) Median DOR, mo: NE (range: 1.4+, 17.4+)
	Breast Cancer[21] Pretreated, advanced or metastatic (168)	ORR:[a] 3% (n=5, 95% CI: 1.0, 6.8) Median DOR, wk: NE (95% CI: 28.7, NE) Median PFS, wk: 5.9 (95% CI: 5.9, 6.0) PFS rate at 24 wk: 10.1% (95% CI: 5.9, 15.5) Median OS, mo: 8.1 (95% CI: 6.4, NE)
	mCRPC[22] Progressed on previous treatment (18)	ORR: 0/18 patients (7 of 18 patients had stable disease >24 weeks post treatment)
	NSCLC[4] 2L metastatic (184)	ORR:[a] 12% (n=22, 95% CI: 7.6, 17.5) Median DOR, wk: NR (0.1, ongoing at 54.1) Median PFS, wk: 11.6 (95% CI: 8.4, 13.7) PFS rate at 48 wk: 18% (95% CI: 12, 26) Median OS, mo: 8.4 (95% CI: 7.3, 10.6) OS rate at 12 mo: 36% (95% CI: 26, 46)
	1L metastatic/recurrent (156)	ORR:[b] 22.4% (n=35, 95% CI: 16.2, 29.8) 68.6% ongoing, median treatment duration 20 weeks Median PFS, wk: 17.6 (95% CI: 11.6, 23.6) PFS rate at 24 wk: 37.2% (95% CI: 28.6, 45.7)
	Ovarian Cancer[4] Pretreated, advanced or metastatic (124)	ORR:[b] 9.7% (n=12, 95% CI: 5.1, 16.3) 50.0% ongoing, median follow-up 12.4 months Median PFS, wk: 11.3 (95% CI: 6.1, 12.0) PFS rate at 48 wk: 5.5% (95% CI: 1.3, 14.2)
	GC/GEJ Cancer[4] Pretreated, advanced or metastatic 1L maintenance (89)	ORR:[b] 9% (n=8, 95% CI: 4.0, 16.9) Median DOR, wk: 48.3 (95% CI: 3.0, NE)
	2L therapy (62)	ORR:[b] 9.7% (n=6, 95% CI: 3.6, 19.9) Median DOR, wk: 12.3 (95% CI: 5.4, NE)
EMR100070-002 (Japan)	**Gastric**[4] Pretreated, metastatic (20)	ORR:[b] 15.0% (n=3, 95% CI: 3.2, 37.9) Median PFS, wk: 11.9 (95% CI: 6.0, 12.3)

+ denotes a censored value
Abbreviations: 1L=first line, 2L=second line, CI: confidence interval, DOR=Duration of response, GC=gastric cancer, GEJ=gastroesophageal junction, mCRPC=metastatic castration resistant prostate cancer, mMCC=metastatic Merkel cell cancer, mo=months, NE=not estimable, NR=not reached, NSCLC=nonsmall cell lung cancer, ORR=objective response rate, PFS=progression free survival, OS=overall survival, SD=stable disease, wk=weeks
a. Considering only confirmed responses.
b. Considering both confirmed and unconfirmed responses.

These studies have also shown an acceptable safety profile for avelumab single agent treatment; most frequently observed treatment-related adverse events from pooled data have been 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%).

While subsets of patients in a growing number of tumor types respond to treatment with a single agent PD-1 or PD-L1 inhibitor, most patients with advanced disease either do not respond to single-agent therapy or experience only a partial response. Further, the majority of those patients who do respond will ultimately progress. These findings of somewhat limited responses are observed regardless of either the PD-1 or PD-L1 inhibitor that is being tested or the tumor type in which the immune checkpoint inhibitor is being evaluated.

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. In the Phase 1 Study PRP-001, in patients treated with talazoparib 1.0 mg/day with advanced breast cancer, ovarian/peritoneal cancer, and pancreatic cancer, an objective response rate (ORR) of 50.0% (7 of 14; 95% confidence interval [CI]: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20% (2 of 10) was observed, respectively.[33] In the ongoing Phase 2 study in patients with locally advanced or metastatic breast cancer harboring BRCA mutations (Study 673-201), independently assessed OR has been observed in 20.8% of 48 patients with disease progression after prior response to platinum-containing regimens and in 37.1% of 35 patients with disease progression after 3 or more non-platinum cytotoxic regimens.

Data from the ongoing EMBRACA study presented in December 2017 (287 patients in talazoparib arm, 144 patients in physician's choice therapy [PCT] arm) showed that 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 (hazard ratio [HR]=0.54; 95% CI: 0.41, 0.71; $p<0.0001$). Also, ORR was 62.6% for talazoparib vs 27.2% for chemotherapy (odds ratio for OR=4.99; 95% CI: 2.9, 8.8; $p<0.0001$; per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1), confirmation of CR/PR was not required) and median duration of response (DOR) was 5.4 months (interquartile range [IQR]: 2.8-11.2) for talazoparib and 3.1 months (IQR: 2.4-6.7) for PCT. The overall survival (OS) data are still immature (38% deaths in each arm) and OS time was not statistically different between arms. The most common adverse events (AEs) observed with talazoparib (>20%, all grade) 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 serious AEs 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.[24]

Talazoparib is proposed for evaluation in combination with avelumab in patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or loss-of-function somatic BRCA1, or BRCA2, or ATM gene defect who have received at least 1 line of standard of care (SOC) treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. This is based on the acceptable safety and pharmacokinetic (PK) profiles observed for each of the investigational products when administered as single agents, on the clinical activity that has been observed for these investigational products, or an agent of the same class, and on proposed complementary mechanisms of action, detailed below.

The activity of avelumab depends on generation of a productive immune response. DNA damage via talazoparib is expected to promote inflammation and prime an immune response by enhancing effective recognition and infiltration of tumors by immune cells. Additionally, talazoparib treatment has been shown to lead to two to three fold increased expression of PD-L1 by tumor cells, suggesting that this may represent a means by which tumors function to inhibit talazoparib-mediated anti-tumor immunity. Based on these interactions between DNA damage, PD-L1 expression and the immune response, the combination of talazoparib and avelumab is expected to lead to additive or synergistic anti-tumor activity.

Preliminary data from other PARP and PD-L1 inhibitor combination studies for treatment of advanced tumors currently tested in clinical trials have shown promising activity and suggest that the combination has an acceptable safety profile.[25,26,45]

This expectation is supported by preclinical studies in syngeneic mouse models of ovarian and colorectal cancers, which demonstrated a significant improvement in overall survival (OS) 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.[40]

Clinical studies have indicated that the greatest sensitivity to PARP inhibitors, such as talazoparib, is observed in tumors with defective repair of DNA double strand breaks (DSBs); such breaks accumulate following PARP inhibition and in the absence of effective repair lead to cell death.[41] One underlying reason for defective DSB repair is the presence of mutations in key genes, either at the germline or somatic level. The BRCA1, BRCA2 and ATM genes are three of the best evidenced examples of such genes. Mutations in either the BRCA1 or BRCA2 gene have been associated with increased response, or improved outcome, following treatment with a number of PARP inhibitors including olaparib, rucaparib, and niraparib while mutations in ATM have been associated with increased response to olaparib.[42,43,44,54] Clinical development of most PARP inhibitors has been focused up to now in tumor types with a relatively high prevalence of BRCA1/2 defects, such as ovarian, breast, prostate and pancreatic cancers. However, analysis of publicly available data within The Cancer Genome Atlas (TCGA[56]), indicates that mutations in BRCA 1/2 and ATM occur with variable frequency in many other tumor types, with an average prevalence across solid tumors of 7.7%. It is expected that all tumors with such defects will present with increased sensitivity to talazoparib mediated DNA damage, and therefore have the potential to benefit from the combination of talazoparib and avelumab.

The primary purpose of this study is to assess the efficacy and safety of the avelumab plus talazoparib combination in approximately 200 patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or somatic BRCA1, or BRCA2, or ATM gene defect who have received at least 1 line of standard of care (SOC) treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. It is anticipated that these patients, who have limited therapeutic options after progression on chemotherapy, and whose tumors harbor sensitizing defects in BRCA 1/2, or ATM, will be most likely to benefit from the combination treatment, independent of their tumor type. There remains a high unmet need in the management of these patients.

Study Objectives and Endpoints

Primary Objective:	Primary Endpoint:
• To evaluate ORR of avelumab in combination with talazoparib, in patients with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.	• Confirmed OR in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by Blinded Independent Central Review (BICR), using RECIST v1.1 (Appendix 3) and, in patients with mCRPC, RECIST v1.1 and PCWG3 (bone) (Appendix 4).
Secondary Objectives:	**Secondary Endpoints:**
• To assess the overall safety and tolerability of avelumab in combination with talazoparib. • To characterize the PK of avelumab and talazoparib when given in combination. • To evaluate the immunogenicity of avelumab when given in combination with talazoparib. • To assess other measures of the anti-tumor activity of avelumab in combination with talazoparib. • To assess the correlation of anti-tumor activity of avelumab in combination with talazoparib with PD-L1 expression in baseline tumor tissue. • To assess the correlation of anti-tumor activity and emergence of resistance with defects in a panel of key oncogenes, including BRCA 1/2 and ATM, and TMB in circulating tumor DNA (ctDNA) and tumor tissue at baseline, during treatment and at the end of treatment.	• Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing. • PK parameters including: pre-dose/trough concentrations (C_{trough}) for avelumab and talazoparib and post-dose concentrations (for talazoparib) and maximum concentrations (C_{max}) for avelumab. • Avelumab Anti-drug antibody (ADA) levels and neutralizing antibodies (Nab) against avelumab. • Confirmed OR as assessed by the investigator, using RECIST v1.1 (Appendix 3) and, in patients with mCRPC, RECIST v1.1 and PCWG3 (Appendix 4). • Time to event endpoints: Endpoints as assessed by BICR and as assessed by the investigator, using RECIST v1.1 (Appendix 3) and in patients with mCRPC, RECIST v1.1 and PCWG3 (Appendix 4), including time to tumor response (TTR), duration of response (DR), and progression free survival (PFS). Additional time-to-event endpoints include overall survival (OS) for all patients and time to prostate-specific antigen (PSA) progression (≥25% increase) for mCRPC patients. • PSA response ≥50% decrease and CTC count conversion for patients with mCRPC. • Cancer antigen (CA)-125 response ≥50% decrease for patients with ovarian cancer. • PD-L1 expression level in baseline tumor tissue. • Presence of defects in a panel of key oncogenes, including BRCA1/2 and ATM, and TMB in ctDNA and tumor tissue at baseline, during treatment, and at the end of treatment.

Study Design

This is a Phase 2b, open-label, multi-center, non-randomized study of avelumab in combination with talazoparib in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors with pathogenic or likely pathogenic germline or loss-of-function somatic BRCA1 or BRCA2, or ATM gene defect who have received at least 1 line of SOC treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. Two cohorts will be enrolled in parallel:

- Cohort 1 will enroll up to approximately 150 patients with locally advanced or metastatic solid tumors with one or more defects in the BRCA1 or BRCA2 genes.

- Cohort 2 will enroll up to approximately 50 patients with locally advanced or metastatic solid tumors with one or more defects in the ATM gene.

Note: in the event that a patient has concomitant defects in more than 1 of the three genes (BRCA1 or BRCA2 or ATM), they will be enrolled in Cohort 1.

Study Treatments

All patients enrolled will receive avelumab and talazoparib.

Avelumab will be administered as a 1-hour IV infusion every 2 weeks (Q2W) on Days 1 and 15 of each 28-day cycle at a dose of 800 mg.

Talazoparib will be self-administered orally once daily (QD) at a dose of 1 mg QD. Patients with moderate renal impairment will receive 0.75 mg QD.

Avelumab will be administered at the investigator site on an outpatient basis. On days when both drugs are administered, talazoparib will be administered first, followed by initiation of the avelumab infusion within 30-60 minutes. See Section 5.4 for premedication and administration details.

Statistical Methods

The primary endpoint is confirmed OR in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by BICR using RECIST v1.1 and, in patients with mCRPC, RECIST v1.1 and PCWG3.

Up to approximately 150 patients will be enrolled in Cohort 1 and 50 patients in Cohort 2. Thus, a total of up to approximately 200 patients will be enrolled.

With 150 and 50 treated patients in Cohort 1 and Cohort 2, respectively, ORR can be estimated with a maximum standard error of 0.041 and 0.071, respectively. Further, assuming a beta (0.5, 0.5) prior,

- Cohort 1: if 66 responders (out of 150 patients, ORR of 43%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.841).

- Cohort 2: if 23 responders (out of 50 patients, ORR of 46%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.807).

Within each cohort, ORR will be estimated and the 2-sided exact 95% confidence intervals (CIs) will be calculated.

An interim analysis will be performed to allow early termination of the cohorts for futility. Within each cohort, ORR based on confirmed partial or complete responses by BICR assessment will be estimated after at least 20 patients are treated and followed for 24 weeks, without holding patient enrollment in either cohort. If based on the observed ORR, the probability of a true ORR ≥40% is ≤0.05 then the cohort will be stopped for futility. For example if 4 or less responders are observed out of 20 patients treated in a cohort (ORR ≤20%) after the minimum follow-up specified above, then the cohort will be stopped for futility.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. 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.

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

Table 1. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)						Post Treatment		
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		End of Treatment[21]	Short-Term Follow-Up (Day 30, Day 60 and Day 90 after last dose)[22]	Long-Term Follow-Up (Every 12 weeks)[23]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)			±3	±3	±3	±3	±3	+7	±7	±14
Informed Consent[1]	X									
Demography	X									
Tumor History[2]	X									
Medical History[3]	X									
Height	X									
Contraception Check[4]	X	X		X		X		X	X	X
Laboratory and Safety Assessments – Must be performed pre-dose during the Treatment Period										
Physical Examination, weight[5]	X	X		X		X		X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X		X		X	X	
Hematology[6]	X	X	X	X	X	X	X	X	X	
Blood Chemistry[6]	X	X	X	X	X	X	X	X	X	
Coagulation[6]	X	As clinically indicated								
Urinalysis[7]	X	As clinically indicated								
Serum/Urine Pregnancy Test *(for women of childbearing potential only)*[8]	X	X		X		X		X		
Hepatitis B and Hepatitis C Virus tests	X									
ACTH and Thyroid Function Tests	X					Every 2 cycles (Cycles 3, 5, 7, etc)		X	X	
Testosterone *(for CRPC patients only)*	X									
12-Lead ECG[9]	X	As clinically indicated								
Enrollment and Treatment										
Enrollment[10]		X								
Talazoparib Administration[11]		Daily								

Table 1. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)						Post Treatment		
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		End of Treatment[21]	Short-Term Follow-Up (Day 30, Day 60 and Day 90 after last dose)[22]	Long-Term Follow-Up (Every 12 weeks)[23]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)			±3	±3	±3	±3	±3	+7	±7	±14
Premedication for Avelumab[12]		X	X	X	X	Optional Administration, at PI discretion, based on presence/severity of prior infusion reactions				
Avelumab Administration[13]		X	X	X	X	X	X			
Tumor Assessments by RECIST (*for all tumor types except CRPC*)[14]	X	Every 8 weeks (±7 days) for 52 weeks from C1D1, then every 16 weeks (±7 days) thereafter until progressive disease as assessed by BICR, regardless of initiation of subsequent anti-cancer therapy								
Tumor Assessments by RECIST *for mCRPC patients ONLY*[14]	X	Every 8 weeks (±7 days) for 24 weeks from C1D1, then every 12 weeks (±7 days) until progressive disease as assessed by BICR, regardless of initiation of subsequent anti-cancer therapy.								
Bone scans, *for mCRPC patients only*	X	Every 8 weeks (±7 days) for 24 weeks from C1D1, then every 12 weeks (±7 days) until progressive disease as assessed by BICR, regardless of initiation of subsequent anti-cancer therapy.								
PSA Tumor Marker Blood Test, *for mCRPC patients ONLY*; pre-dose	X	X		X		X				
Blood Test for circulating tumor cells (CTC) (*for mCRPC patients ONLY*)		X		X		X[15]				
CA-125 Tumor Marker Blood Test (*for ovarian cancer patients ONLY*)	X	X		X		X				
Other Clinical Assessments										
Serious and Non-Serious Adverse Event Monitoring[16]	X	Monitored and recorded continually						X	X	
Concomitant Treatments[17]	X	Monitored and recorded continually						X	X	
Subsequent Anti-Cancer Treatment									X	X
Survival										X[20]
Patient-Reported Outcomes										
EORTC QLQ-C30, EORTC QLQ-BR23, EORTC QLQ-OV28, EORTC QLQ-PR25, EQ-5D-5L[18]		X	X	X	X	X	X	X	X	

Table 1. Schedule of Activities: Safety and Efficacy Assessments

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)						Post Treatment		
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		End of Treatment[21]	Short-Term Follow-Up (Day 30, Day 60 and Day 90 after last dose)[22]	Long-Term Follow-Up (Every 12 weeks)[23]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)			±3	±3	±3	±3	±3	+7	±7	±14
PRO-CTCAE™[19]		X	Every 7 days during treatment period					X	X	

ACTH=adrenocorticotropic hormone, C=Cycle; C1D1=Cycle 1 Day 1; CA-125=Cancer antigen 125; CRPC=castration-resistant prostate cancer; CTC: circulating tumor cells; CTCAE = Common Terminology Criteria for Adverse Event; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC = The European Organization for Research and Treatment of Cancer; PI=principal investigator; PRO = Patient Reported Outcomes.

Footnotes for Safety and Efficacy Assessments Schedule of Activities:

1. **Informed Consent**: Must be obtained prior to undergoing any study-specific procedure and may be obtained >28 days prior to enrollment.
2. **Tumor History**: Tumor history includes oncology history such as information on tumor diagnosis, including existing PD-L1, BRCA1, BRCA2 and ATM testing results, prior regimens (duration of administration, best overall response [BOR] observed, and recurrence date), surgery, and radiation therapy. Gleason score (from initial diagnosis) is collected for mCRPC.
3. **Medical History:** Medical history includes history of diseases or injuries (active or resolved) and concomitant illnesses that are not considered to be the disease under study.
4. **Contraception Check:** Investigator to confirm the patient has been instructed in correct use of highly effective contraception, as applicable and for the duration as detailed in Sections 4.3. See also Section 7.1.2.
5. **Physical Examination:** Full physical examination at screening. Subsequent visits to include major body systems (focused and/or as clinically indicated); baseline physical exam may be performed with 1 day window before treatment. See Section 7.1.5.
6. **Hematology, Coagulation, Blood Chemistry, ACTH and Thyroid Function Tests:** Required safety laboratory tests including at a minimum: hematology (hemoglobin, platelets, and white blood cells), and chemistry (ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose) must be reviewed prior to study drug administration on Days 1 and 15 of each treatment cycle. See Section 7.1.4 for the list of required Laboratory Tests and Section 5.4.6 for requirements to perform additional laboratory tests to monitor toxicity related to either investigational product. It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to C1D1 as part of Screening.
7. **Urinalysis:** See Section 7.1.4.
8. **Serum/Urine Pregnancy Test (*for women of childbearing potential only*):** Pregnancy test results must be reviewed prior to study drug administration on Days 1 of each treatment cycle. See Section 4.1 for criteria defining women of childbearing potential. See Section 7.1.1 for additional pregnancy testing details.
9. **12-Lead ECG:** See Section 7.1.6 for details regarding ECGs and the procedure to follow if mean QTc is prolonged (>500 msec).
10. **Enrollment:** Patients meeting all entry criteria will be enrolled using the Interactive Response Technology (IRT) system and will initiate investigational product administration preferably on the same day as enrollment (investigational product administration must begin within 3 days after enrollment). See Section 5.1.
11. **Talazoparib Administration:** See Section 5.4.2 for details. On Day 1 and Day 15 of each 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 before the avelumab infusion. Drug supply must be taken into account when scheduling visits, taking the visit windows into consideration.
12. **Premedication for Avelumab:** See Section 5.4.3 for details on the premedication and Section 5.4.1 on the administration of the study combination treatment.

13. **Avelumab Administration:** After the patient has taken talazoparib and the premedication was administered, avelumab 800 mg IV as a 1-hour infusion must start 30-60 minutes after the premedication. See Section 5.4.4.1 for special precautions for avelumab administration.
14. **Tumor Assessments:** See Section 7.6 for details on tumor assessments using RECIST version 1.1 (See Appendix 3) and, for mCRPC patients, PCWG3 (See Appendix 4). Brain and bone imaging are mandatory at baseline. Baseline scans are to be performed within 28 days prior to the first dose of study treatment. Imaging should be performed with contrast agents unless contraindicated for medical reasons. Timing of disease assessment should follow calendar days and should not be adjusted for delays in cycle starts. Tumor assessments should also be performed whenever disease progression is suspected. For tumor types other than mCRPC, if bone metastases are present at baseline (screening), then repeat bone imaging is required every 16 weeks during the first 52 weeks of study treatment and every 24 weeks thereafter.
15. **CTC Blood Test**: Blood sample for CTCs will be collected on Day 1 of Cycles 3 and 4 (in addition to Day 1 of Cycles 1 and 2). See Section 7.7.3 for additional details.
16. **Serious and Non-Serious Adverse Event Monitoring:** See Section 8 for guidance on the time period for collecting and reporting AE and SAEs.
17. **Concomitant Treatments:** See Section 5.7 for additional details on concomitant treatments; see Section 5.7.10 for prohibited medications.
18. **Patient reported outcomes (PRO):** The ePRO device training is to be provided to the patients at enrollment and the site coordinator should ensure patient understanding and ability to use the device. Patients must complete these questionnaires using the ePRO device at the clinic prior to any study or medical procedure during Day 1 Cycle 1, and then complete all subsequent assessments at home using the ePRO device. These assessments are not required to be completed if a patient does not understand the language(s) available for a specific questionnaire and cannot complete the specific questionnaire independently. See Section 7.8.

    EORTC QLQ-C30 and EQ-5D-5L will be collected in all patients from both Cohorts 1 and 2. The following will be collected as per tumor type and only from Cohort 1: EORTC QLQ-BR23 (breast cancer patients only), EORTC QLQ-OV28 (ovarian cancer patients only), EORTC QLQ-PR25 (prostate cancer patients only).
19. **PRO-CTCAE**: All patients in countries where the PRO-CTCAE translations are currently available. Patients must complete this questionnaire using the ePRO device at the clinic prior to any study or medical procedure during Day 1 Cycle 1, and then complete all subsequent assessments at home using the ePRO device and for short-term follow-up only for Day 30. These assessments are not required to be completed if a patient does not understand the language(s) available for a specific questionnaire and cannot complete the specific questionnaire independently. See Section 7.8.6.
20. **Survival:** See Section 6.5 for Long-Term Follow-up.
21. **End of Treatment:** Perform tests/procedures if not completed during the previous 7 days.
22. **Short-term Follow-up Serious and Non-Serious Adverse Event Monitoring:** See Section 6.4.
23. **Long-Term Follow-up:** See Section 6.5.

Table 2. Schedule of Activities: Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)						Post Treatment		
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		End of Treatment	Short-Term Follow-Up (Day 30, Day 60 and Day 90 after last dose)	Long-Term Follow-Up (Every 3 months)
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15			
Visit Window (Days)			±3	±3	±3	±3	±3	+7	±7	±14
Pre-treatment tumor tissue[1]	X									
Blood Draw for DNA Analysis[2]		X								
Blood Draw for Talazoparib PK[3]		X	X			Cycle 3 only				
Blood Draw for Avelumab PK[4]		X	X			Cycles 3, 6, 12, 18, and 24 only				
Blood Draw for Immunogenicity (ADA) Testing[5]		X	X			Cycles 3, 6, 12, 18, and 24 only		X		
Blood draw for Genomic Banked Biospecimen Prep D1[6]		X								
Blood draw to generate plasma for circulating tumor (ct)DNA analysis[7]		X		X		Cycle 3 only		X		
Blood draw to generate plasma for Biomarker/Proteomic/Metabolomic Analysis[8]		X						X		
Blood Draw for TCR Analysis[9]		X	X	X				X		
Blood Draw for RNA analysis[10]		X						X		
Tumor Biopsy[11]		Optional						X[12]		

ADA=anti-drug antibodies; BRCA=BReast CAncer susceptibility gene; ATM=ataxia telangiectasia mutated; C=Cycle; C1D1=Cycle 1 Day 1; DNA=deoxyribonucleic acid; PI=principal investigator; PK=pharmacokinetics; RNA=ribonucleic acid; TCR=T-cell receptor

Footnotes for Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments Schedule of Activities:

Please refer to Laboratory Manual for instructions on sample collection, processing and shipment for all Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic tests listed in Table 2.

1. **Pre-treatment Tumor Tissue:** All patients must submit fresh or recent formalin-fixed paraffin-embedded (FFPE) tumor tissue sample as described in Section 7.4.1.1. Availability of tumor tissue sample must be confirmed during screening prior to enrollment, and sample must be sent within 28 days after enrollment.
2. **Blood Draw for DNA Analysis**: A 4-mL whole blood biospecimen will be collected prior to dosing on Day 1 of Cycle 1. See Section 7.4.2.
3. **Blood Draw for Talazoparib PK:** Blood samples (3-mL whole blood) will be collected at pre-dose (within 1 hour prior to taking talazoparib dose); and at the end of the avelumab infusion (within 10 minutes after the avelumab infusion ends) on Day 1 and Day 15 of Cycle 1, and then on Day 1 of Cycle 3. See Section 7.2.2.
4. **Blood Draw for Avelumab PK:** Blood samples (3.5-mL whole blood) will be collected at pre-dose (within 1 hour prior to taking talazoparib dose) and at the end of infusion (within 10 minutes after the avelumab infusion ends) on Day 1 and Day 15 of Cycle 1, on Day 1 of Cycles 3, 6, 12, 18, and 24. See Section 7.2.1.

5. **Blood Draw for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5-mL whole blood) for avelumab immunogenicity testing will be collected pre-dose on Day 1 and Day 15 of Cycles 1, on Day 1 of Cycle 3 and then on Day 1 of Cycles 6, 12, 18, 24, and at the EOT. See Section 7.3.
6. **Blood draw for Genomic Banked Biospecimen Prep D1**: A 4-mL whole blood sample will be collected on Day 1 of Cycle 1 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. See Section 7.5.
7. **Blood draw to generate plasma for ctDNA:** A 20 mL whole blood specimen for processing to plasma will be collected on Day 1 of Cycle 1, 2 and 3 and at EOT. See Section 7.4.2.
8. **Blood draw to generate plasma for Biomarker/Proteomic/Metabolomic Analysis**: A 4-mL whole blood biospecimen for processing to plasma will be collected at Day 1 Cycle 1 and at EOT. See Section 7.4.2.
9. **Blood Draw for TCR Sequencing Analysis:** A 6-mL whole blood sample will be collected into a tube optimized for deoxyribonucleic acid (DNA) preservation on Days 1 and 15 of Cycle 1, Day 1 of Cycle 2 and at EOT. See Section 7.4.2.
10. **Blood Draw for RNA Analysis**: Two 2.5-mL whole blood samples will be collected in designated tube to optimize sample for RNA analysis on Day 1 of Cycle 1 and at EOT. See Section 7.4.2.
11. **Tumor Biopsy during Treatment Period (Optional):** Tumor tissue is requested for study purposes for patients who undergo tumor biopsy or resection as part of routine clinical care at any time during the treatment period. See Section 7.4.1.2.
12. **Tumor Biopsy at End of Treatment:** Every effort should be made to obtain EOT (±14 days) biopsies in cases of RECIST v1.1 or PCWG3 confirmed disease progression if a patient discontinues study treatment due to disease progression, except in instances where the procedure, as performed in the clinical research setting, poses an unacceptable risk to the patient. See Section 7.4.1.2.

1. INTRODUCTION

This is a Phase 2 study to assess the safety and efficacy of the avelumab plus talazoparib combination in up to approximately 200 patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or somatic BRCA1, BRCA2, or ATM gene defect, as determined by local assessment and classification. Patients with these gene defects have limited therapeutic options after their disease has progressed on standard of care (SOC) chemotherapy. It is anticipated that patients with tumors harboring defects in the BRCA1, BRCA2, or ATM gene will likely benefit from treatment with the combination of avelumab plus talazoparib, independent of their tumor type, and that the combination may produce additive or synergistic anti-tumor activity relative to each drug used as a single agent.

1.1. Mechanism of Action/Indication

1.1.1. Avelumab

Avelumab is a human immunoglobulin (Ig)G1 mAb directed against PD-L1. Avelumab selectively binds to PD-L1 and competitively blocks its interaction with programmed death receptor 1 (PD-1), thereby interfering with this key immune checkpoint pathway. Compared with anti-PD-1 antibodies that target T cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the programmed death ligand 2 (PD-L2)/PD-1 pathway intact to promote peripheral self-tolerance.[1,2] For complete details of the in vitro and nonclinical studies, refer to the avelumab Investigator's Brochure (IB).[4] In March 2017, avelumab received accelerated approval by the United States (US) Food and Drug Administration (FDA) as the first treatment for metastatic Merkel cell carcinoma (mMCC);[5] this was followed by approvals in the European Union (EU), Switzerland, Japan, Australia, Israel and Canada.[6,7,8] In May 2017, avelumab received accelerated approval by the US FDA for the treatment of patients with locally advanced or metastatic UC with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.[5] Avelumab is currently being investigated as single agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors and various hematological malignancies.

While subsets of patients in a growing number of tumor types respond to treatment with a single agent PD-1 or PD-L1 inhibitor, most patients with advanced disease either do not respond to single agent therapy or experience only a partial response. Further, the majority of those patients who do respond will ultimately progress. These findings of somewhat limited responses are observed regardless of either the PD-1 or PD-L1 inhibitor that is being tested or the tumor type in which the immune checkpoint inhibitor is being evaluated.

Additional information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[4]

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.[9,10,11] Although other PARP inhibitors also possess both activities, in vitro studies demonstrated that talazoparib has more potent PARP trapping activity than other PARP inhibitors in clinical development.[10,12]

DNA damage promotes inflammation via the NF-κB pathway[13] and the stimulation of interferon genes (STING) pathway,[14,15] 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).[16,17] 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.[18] Additionally, talazoparib treatment has been shown to lead to increased expression of PD-L1 by tumor cells,[20] suggesting that this may represent a means by which tumors function to inhibit talazoparib-mediated anti-tumor immunity.

Talazoparib is currently being investigated as single agent and in combination with other anti-cancer therapies in patients with locally advanced or metastatic solid tumors. Talazoparib was approved by the FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.

Additional information for talazoparib may be found in the SRSD, which for this study is the talazoparib IB.[23]

1.2. Background and Rationale

1.2.1. Avelumab Clinical Experience

Avelumab is being developed jointly by Pfizer and Merck KGaA/EMD Serono and is indicated for the treatment of adults and pediatric patients 12 years and older with mMCC and in adult patients having UC with disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Avelumab is also being studied in a wide variety of cancers, including NSCLC, gastric cancer, renal cell carcinoma (RCC), ovarian cancer, UC, Hodgkin's Lymphoma, 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 (IV) as single agent at a dose of 10 mg/kg every 2 weeks (Q2W) has been characterized primarily in 1738 adult patients from studies EMR100070-001 in various solid tumors (N=1650) and EMR100070-003 Part A in mMCC (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, in total, 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, CRPC, adrenocortical carcinoma, melanoma, mesothelioma, UC, ovarian cancer, RCC, and squamous cell cancer of the head and neck. Study EMR100070-003 Part A was conducted in patients with mMCC.

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 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 patients, with no clear relationship between the duration of immunogenicity response and the maximum observed titer. Current data suggest there is no clinically meaningful impact of ADA positivity on the pharmacokinetics (PK), efficacy, or safety of avelumab.

1.2.1.1. Clinical Experience in Patients with Solid Tumors

In Study EMR100070-001, avelumab as a single agent has been evaluated for efficacy in patients with multiple types of solid tumors (see Table 1). The study includes efficacy data from a cohort of 156 patients with advanced NSCLC who had not been previously treated systemically for metastatic or recurrent disease and were without an activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement; a separate cohort enrolled 184 patients with advanced NSCLC who had progressed after at least 1 line of platinum-containing doublet chemotherapy for metastatic or locally advanced disease. A cohort of 161 patients with locally advanced or metastatic UC were either cisplatin ineligible or had progressive disease (PD) after at least 1 line of platinum-based therapy in 2 different cohorts. A cohort of 124 patients with recurrent or refractory ovarian cancer were enrolled who had progression within 6 months of platinum-based therapy or progression after subsequent therapy in previous relapse. A cohort included 168 patients were enrolled with metastatic breast cancer refractory to or progressing after standard-of-care therapy; 72 patients (42.9%) were human epidermal growth factor receptor 2 (HER2)-negative and estrogen receptor (ER)-positive or progesterone receptor-positive, 58 patients (34.5%) were triple-negative breast cancer (TNBC), 26 patients (15.5%) were HER2-positive, and 12 patients (7.1%) had unknown biomarker status. Other cohorts included 151 patients with advanced GC/GEJ who were treated with avelumab, either as first-line maintenance (89 patients) or second-line therapy (62 patients), and 18 patients with mCRPC.[22]

Study EMR 100070-001 also provides preliminary avelumab efficacy data from 53 patients with advanced mesothelioma (ORR 9.4%; 95% CI: 3.1, 20.7) and 37 patients with adrenocortical carcinoma (ORR 10.5%; 05% CI: 1.3, 33.1%). Further details are available in the IB.

Preliminary efficacy data for the ongoing Phase 1 Trial EMR100070-002 are available from a data cutoff of 11 March 2015 for 20 patients being treated with 10 mg/kg of avelumab once every 2 weeks in the gastric cancer expansion cohort. All 20 patients are Japanese patients. PK, pharmacodynamics and safety and efficacy results are consistent with other global studies.

Trial EMR100070-003 enrolled 88 patients with mMCC whose disease had progressed after at least one prior line of chemotherapy in the metastatic setting. The median follow-up was 10.4 months (range of 6.0 to 19.3). The confirmed ORR was 31.8% (95% CI: 21.9, 43.1), consisting of 8 complete responses (CRs) and 20 partial responses (PRs). Responses to avelumab were durable, with median duration of response not yet reached (95% CI: 8.3 months – not estimable).

Table 3. Avelumab: Efficacy Results

Study	Tumor Type (n)	Efficacy Results
EMR100070-003 (JAVELIN Merkel 200)	**mMCC**[5] 2L, pretreated, metastatic (88)	ORR:[a] 33.0% (n=29, 95% CI: 23.3, 43.8) DOR range, mo: 2.8, 23.3+
EMR100070-001	**Urothelial Carcinoma**[5] Pretreated, advanced or metastatic (161, with ≥6 mo follow-up)	ORR:[a] 16.1% (n=26, 95% CI: 10.8, 22.8) Median DOR, mo: ongoing (95% CI: 1.4+, 17.4+)
	Breast Cancer[21] Pretreated, advanced or metastatic (168)	ORR:[a] 3% (n=5, 95% CI: 1.0, 6.8) Median DOR, wk: NE (95% CI: 28.7, NE) Median PFS, wk: 5.9 (95% CI: 5.9, 6.0) PFS rate at 24 wk: 10.1% (95% CI: 5.9, 15.5) Median OS, mo: 8.1 (95% CI: 6.4, NE)
	mCRPC[22] Progressed on previous treatment (18)	ORR: 0/18 patients (7 of 18 patients had stable disease >24 weeks post treatment)
	NSCLC[4] 2L metastatic (184)	ORR:[a] 12% (n=22, 95% CI: 7.6, 17.5) Median DOR, wk: NR (0.1, ongoing at 54.1) Median PFS, wk: 11.6 (95% CI: 8.4, 13.7) PFS rate at 48 wk: 18% (95% CI: 12, 26) Median OS, mo: 8.4 (95% CI: 7.3, 10.6) OS rate at 12 mo: 36% (95% CI: 26, 46)
	1L metastatic/ recurrent (156)	ORR:[b] 22.4% (n=35, 95% CI: 16.2, 29.8) 68.6% ongoing, median treatment duration 20 weeks Median PFS, wk: 17.6 (95% CI: 11.6, 23.6) PFS rate at 24 wk: 37.2% (95% CI: 28.6, 45.7)
	Ovarian Cancer[4] Pretreated, advanced or metastatic (124)	ORR:[b] 9.7% (n=12, 95% CI: 5.1, 16.3) 50.0% ongoing, median follow-up 12.4 months Median PFS, wk: 11.3 (95% CI: 6.1, 12.0) PFS rate at 48 wk: 5.5% (95% CI: 1.3, 14.2)
	GC/GEJ Cancer[4] Pretreated, advanced or metastatic 1L maintenance (89)	ORR:[b] 9% (n=8, 95% CI: 4.0, 16.9) Median DOR, wk: 48.3 (95% CI: 3.0, NE)
	2L therapy (62)	ORR:[b] 9.7% (n=6, 95% CI: 3.6, 19.9) Median DOR, wk: 12.3 (95% CI: 5.4, NE)
EMR100070-002 (Japan)	**Gastric**[4] Pretreated, metastatic (20)	ORR:[b] 15.0% (n=3, 95% CI: 3.2, 37.9) Median PFS, wk: 11.9 (95% CI: 6.0, 12.3)

+ denotes a censored value

Abbreviations: 1L=first line, 2L=second line, CI: confidence interval, DOR=Duration of response, GC=gastric cancer, GEJ=gastroesophageal junction, mCPRC=metastatic castration resistant prostate cancer, mMCC=metastatic Merkel cell cancer, mo=months, NE=not estimable, NR=not reached, NSCLC=nonsmall cell lung cancer, ORR=objective response rate, PFS=progression free survival, OS=overall survival, SD=stable disease, wk=weeks

a. Considering only confirmed responses.
b. Considering both confirmed and unconfirmed responses.

1.2.1.2. 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 patients 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.

1.2.2. Talazoparib

1.2.2.1. Talazoparib Clinical Experience

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

As of 31 Janurary 2018, approximately 659 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 BReast CAncer (BRCA) 1 or BRCA 2 defect, a Phase 3 study (673-301) in locally advanced or metastatic breast cancer

with a germline BRCA 1/2 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).[23]

As of 31 January 2018, aggregate safety data from 5 company-sponsored clinical studies evaluating talazoparib monotherapy at the proposed dose of 1 mg QD in patients with advanced malignancies ((PRP-001, 673-201, 673-301, MDV3800-13, and MDV3800-14; 502 patients total) provide the basis for the most common TEAEs. The most common study drug-related TEAEs associated with talazoparib (>20%) occurring in patients who received 1 mg QD talazoparib were anemia (45.8%), fatigue (36.1%), nausea (32.5%), neutropenia (21.9%), and alopecia (20.1%). The most common Grade 3 or higher drug-related TEAEs occurring in ≥5% of patients were anemia (34.1%), neutropenia (12.2%). thrombocytopenia (10.6%), and platelet count decreased (5.4%).

Serious adverse events (SAEs) occurred in 164 of 502 patients (32.7%) who received talazoparib 1 mg QD. SAEs occurring in ≥2% of patients were anemia (5.2%) and dyspnea and pleural effusion (2.2% each). Forty-seven patients had SAEs considered related to talazoparib. Study drug-related SAEs occurring in ≥1% of patients were anemia (4.6%); thrombocytopenia (1.2%); and platelet count decreased (1.2%). A total of 23 of 502 patients who received 1 mg QD talazoparib had a TEAE that led to death (8 associated with the underlying malignancy including 1 also associated with pneumonia; 2 dyspnea; and 2 general physical health deterioration, 3 disease progression, and 1 each lung infection, cerebral hemorrhage, cerebrovascular accident, fatigue (after data cutoff date of 31 January 2018 the AE of Grade 5 fatigue was changed to Grade 5 failure to thrive), liver disorder, neurological symptom, respiratory failure, and veno-occlusive disease). Of these events, only veno-occlusive disease was assessed as related to talazoparib. A 34 year old female patient with advanced breast cancer metastatic to the axilla and bone developed asymptomatic Grade 3 liver test abnormalities (ALT and AST with normal bilirubin) while receiving talazoparib at 0.75 mg. 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. The sponsor considered veno occlusive disease of the liver an unlikely etiology, a consideration supported by 2 independent hepatologists who reviewed the case.

Among the 502 patients who received 1 mg QD talazoparib, 63.9% had a TEAE that led to dose reduction and 61.2% had a TEAE that led to dose interruption. The most common TEAEs that led to dose reduction or interruption were associated with myelosuppression.

Twenty of 502 patients (4.0%) 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 (3 patients), increased ALT (2 patients), and accidental overdose, increased AST, metastatic breast cancer, cerebral hemorrhage, dyspnea, glioblastoma multiforme, headache, metastases to meninges, muscular weakness, neutropenia, obstructive airways disorder, thrombocytopenia, transient ischemic attack, and vomiting (1 patient each).[23]

1.2.2.2. Clinical Efficacy in Patients with Advanced Solid Tumors

A total of 110 patients with advanced tumors with DNA repair pathway abnormalities, particularly those associated with BRCA 1/2 and phosphatase tensin homolog (PTEN) dysfunction, were enrolled in the Phase 1 study PRP-001, which was completed in March 2015. The maximum tolerated dose (MTD) of talazoparib was defined as 1 mg QD and it was used in the expansion phase of the study in patients with breast, ovarian/primary peritoneal, and pancreatic cancer with deleterious germline mutations; small cell lung cancer (SCLC); and Ewing sarcoma. In the Phase 1 Study PRP-001, in patients treated with talazoparib 1.0 mg/day with advanced breast cancer, ovarian/peritoneal cancer, and pancreatic cancer, an ORR of 50.0% (7 of 14; 95% CI: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20% (2 of 10) was observed, respectively.[23]

1.2.2.2.1. Clinical Efficacy in Patients with Germline BRCA 1/2 Mutations and Locally Advanced and/or Metastatic Breast Cancer

The ongoing Phase 2, open-label, 2-stage, 2-cohort study, 673-201, is evaluating talazoparib in patients with locally advanced or metastatic breast cancer with deleterious germline BRCA 1/2 mutations. Enrolled patients included those who were platinum-sensitive (Cohort 1) and patients who received at least 3 prior chemotherapy regimens and no prior platinum therapy (Cohort 2). As of 01 September 2016, the data cut-off for the primary analysis, 83 patients with locally advanced or metastatic breast cancer with deleterious germline BRCA 1/2 mutations were tumor evaluable (48 patients in Cohort 1; 35 patients in Cohort 2), and 9 patients were continuing on treatment. Efficacy analyses were conducted by independent central radiology assessment. The ORR was 20.8% (95% CI: 10.47, 34.99) in Cohort 1, 37.1% (95% CI: 21.47, 55.08) in Cohort 2 and 27.7% (95% CI: 18.45, 38.62) overall. This response rate, which included 2 CRs and 8 PRs in Cohort 1 and 13 PRs in Cohort 2, is considered clinically meaningful as these populations have a poor prognosis.[23]

Data from the ongoing EMBRACA study presented in December 2017 (287 patients in talazoparib arm, 144 patients in PCT arm) showed that 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; $p<0.0001$). Also, ORR was 62.6% for talazoparib vs 27.2% for chemotherapy (odds ratio for OR=4.99; 95% CI: 2.9, 8.8; $p<0.0001$; per RECIST 1.1, confirmation of CR/PR was not required) and median duration of response (DOR) was 5.4 months (IQR: 2.8-11.2) for talazoparib and 3.1 months (IQR: 2.4-6.7) for PCT. The OS data are still immature (38% deaths in each arm) and OS time was not statistically different between arms.[24]

1.2.2.3. Pharmacokinetics of Talazoparib in Humans

Talazoparib plasma exposure was dose proportional in the dose range of 0.025 mg to 2 mg QD suggesting linear PK. Talazoparib absolute bioavailability is at least 54.6%. After administration of a single 1 mg dose of talazoparib to cancer patients, the median Time to Maximum Plasma Concentration (T_{max}) ranged from 0.5 to 2.0 hours across studies. Administration of talazoparib with food (a high-fat, high-calorie meal) had no impact on the Area Under the Curve (AUC) while food reduced the Maximum Plasma Concentration

(C_{max}) by 46%. The reduction in the rate of absorption with food is not expected to be clinically relevant as efficacy is driven by total exposure. Therefore, talazoparib can be taken without regard of food.

Mean talazoparib binding to human plasma proteins is 74%. Population PK analysis showed that talazoparib apparent steady-state volume of distribution (Vss/F) was 420 L, which is greater than total body water (42 L), indicating that talazoparib extensively distributes to peripheral tissues.

Talazoparib undergoes minimal hepatic metabolism. Based on population PK analysis, there was no effect of mild hepatic impairment (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferanse [AST] >ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) on talazoparib exposure. No dose adjustment is necessary for patients with mild hepatic impairment. The effect of hepatic impairment on talazoparib PK is being investigated in the ongoing study MDV3800-02.

Talazoparib was eliminated slowly with a mean terminal plasma half-life (t½) of 89.8 hours. Talazoparib accumulated after 1 mg QD dosing with a median accumulation ratio, based on AUC ranging from 2.33 to 5.15, consistent with its t½. Population PK analysis showed that talazoparib apparent oral clearance (CL/F) was 6.45 L/hr. Excretion of unchanged talazoparib in urine was the major route of elimination accounting for 54.6% of the administered dose. Population PK analysis showed that talazoparib CL/F was reduced by 14.4% and 37.1% in patients with mild renal impairment (creatinine clearance [CrCl], 60-89 mL/min) and moderate renal impairment (30 mL/min ≤ CrCl <60 mL/min), respectively, compared to that of patients with normal renal function (CrCl >90 mL/min). No dose adjustment is recommended for patients with mild renal impairment. The starting dose of talazoparib for patients with moderate renal impairment is discussed in Section 1.2.5.2. The effect of renal impairment on talazoparib PK is being investigated in the ongoing study MDV3800-01.

In vitro studies showed that talazoparib is a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). 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. Guidelines for concomitant use of talazoparib with P-gp inhibitors or inducers and BCRP inhibitors are provided in Section 5.7.10.

1.2.3. Clinical Experience in Patients Treated with Other PARP Inhibitors as a Single Agent or in Combination with Immunotherapy

Reports of clinical activity from other agents of the same class as talazoparib, alone and in combination with other immunotherapies, support the investigation of talazoparib with avelumab for the treatment of tumors with high prevalence of BRCA 1/2 or ATM in similar therapeutic setting. Clinical data is summarized below by tumor type.

1.2.3.1. PARP Inhibitor Experience in Ovarian Cancer (OC)

OC is most frequently diagnosed at an advanced stage, and despite high response rates to initial taxane-platinum-based chemotherapy, the majority of patients will develop persistent or recurrent disease. There remains a particularly urgent unmet need for well-tolerated treatments which will improve outcomes for patients who have received multiple lines of chemotherapy.

Olaparib has been approved as monotherapy in patients with deleterious or suspected deleterious germline BRCA 1/2-mutated advanced OC who have been treated with three or more prior lines of chemotherapy. From a Phase 2 single-arm study in which 137 patients with BRCA 1/2- mutated OC who had received ≥3 prior lines of chemotherapy were administered olaparib monotherapy until disease progression or intolerable toxicity, the ORR was 34% (46 of 137 patients; 95% CI: 26%-42%), and the median duration of response was 7.9 months (95% CI: 5.6-9.6). ORR in platinum-resistant tumors was 30%. Median DoR for platinum-sensitive and platinum-resistant disease was similar: 8.2 months (95% CI: 5.6-13.5) compared with 8.0 months (95% CI: 4.8–14.8), respectively.[27] Olaparib is being further evaluated in combination with the PD-L1 inhibitor durvalumab in a Phase 1 dose-escalation study in women's cancers and found to provide durable anti-cancer activity in heavily pretreated patients; three of four women with BRCA wild-type platinum-resistant ovarian carcinoma had durable responses of ≥9 months. No dose-limiting toxicities were observed.[25]

Rucaparib has been approved for the treatment of patients with deleterious BRCA 1/2 mutation (germline and/or somatic) associated advanced OC who have been treated with two or more chemotherapies. Approval was based on data from two multicenter, single-arm, open label clinical trials that evaluated the efficacy of rucaparib in 106 patients with advanced ovarian cancer who had progressed after treatment with two or more prior chemotherapies. Investigator-assessed ORR was 54% (57/106; 95% CI: 44-64%). Median DoR for the 57 responders (investigator-assessed) was 9.2 months (95% CI: 6.6, 11.6). ORR (investigator-assessed) was 66% (52/79; 95% CI: 54-76%) in platinum-sensitive patients, 25% (5/20; 95% CI: 9-49%) in platinum-resistant patients and 0% (0/7; 95% CI: 0-41%) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation.[28]

Preliminary phase 1 data from the combination of niraparib with PD-1 inhibitor pembrolizumab (TOPACIO) in patients with platinum resistant OC has shown preliminary efficacy (response in 5 of 9 patients) with no significant overlapping toxicity.[29] As of August 2017, in the ongoing Phase 2 study, 5 of 27 TNBC patients and 6 of 29 OC patients had a ≥30% decrease in tumor lesion size; no new safety signals were identified.[30]

1.2.3.2. PARP Inhibitor Experience in Advanced Breast Cancer

Several Phase 1 and 2 studies have shown that PARP inhibitors have single-agent activity in patients with metastatic breast cancer and a germline BRCA 1/2 mutation.[31,32,33]

The randomized, Phase 3 OlympiAD trial showed that, among patients with HER2-negative metastatic breast cancer and a germline BRCA 1/2 mutation, progression-free survival (PFS) was significantly longer with single-agent PARP inhibitor olaparib than with standard chemotherapy (capecitabine, eribulin mesylate, or vinorelbine) (median PFS 7.0 months vs. 4.2 months; hazard ratio (HR) for PFS= 0.58; 95% CI: 0.43 - 0.80). The response rate in the olaparib group was approximately double the rate in the standard-therapy group (59.9% vs. 28.8%).[34]

The MEDIOLA study with the combination of olaparib and PD-L1 inhibitor durvalumab demonstrated a disease control rate of 80% (90% CI 62-92%) and ORR of 52% (95% CI, 31%-72%) in 25 pretreated BRCA-mutant metastatic breast cancer patients; no enhanced toxicity was observed with olaparib and no change was seen from the expected toxicity of durvalumab.[26]

For efficacy evidence of talazoparib in advanced breast cancer with germline BRCA 1/2 mutations please see Section 1.2.2.2.

1.2.3.3. PARP Inhibitor Experience in Metastatic Castration Resistant Prostate Cancer (mCRPC)

Olaparib given as single agent was evaluated in a Phase 2 study in 50 patients with previously treated mCRPC.[43] Of the 50 patients, all patients had received prior treatment with docetaxel, 49 (98%) had received abiraterone or enzalutamide, and 29 (58%) had received cabazitaxel. Of the 49 patients evaluable for response (defined either as an objective response according to RECIST v1.1, or as a reduction of at least 50% in the prostate-specific antigen (PSA) level or a confirmed reduction in the circulating tumor-cell count from 5 or more cells per 7.5 mL of blood to less than 5 cells per 7.5 mL), 16 patients achieved a response (33%; 95% CI: 20.0, 48.0), including patients previously treated with docetaxel. Homozygous deletions, deleterious mutations, or both were identified in DNA-repair genes in 16 patients (33%) and 14 of these patients (88%) achieved a response.

The combination of olaparib with durvalumab is under evaluation in a Phase 1/2 study patients with mCRPC. Overall, 5 out of 7 patients have had a reduction in PSA level ≥50% from baseline. Based on data thus far, the combination appears to have an acceptable safety profile.[45]

1.2.3.4. PARP Inhibitor Experience in Pancreatic Cancer

In a multicenter Phase 2 study evaluating responses to PARP inhibitor olaparib across different tumor types associated with germline BRCA 1/2 mutations and recurrent cancer, 23 patients with advanced pancreatic cancer were enrolled. 17 (74%) had a BRCA2 mutation, and one had a mutation in both BRCA1 and BRCA2. The mean number of prior therapies was two (standard deviation= 1.6; range: 1-8); all but one patient had received gemcitabine, and 65% had received prior platinum.

Median PFS was 4.6 months. ORR was 22% (95% CI: 7.5, 43.7). Stable disease that persisted ≥8 weeks was observed in 34.8% of patients (n= 8; 95% CI: 16.4, 57.3). Median duration of response was 134 days. There was no apparent difference in response rates in those with (20%; 95% CI: 4.3, 48.1) or without (25%; 95% CI: 3.2, 65.1) prior platinum for pancreatic cancer. Median OS was 9.8 months.[32]

Rucaparib also showed promise in a Phase 2 study in previously treated patients with pancreatic cancer who have the mutation.[27] Overall, a clinical benefit was observed in 32% of patients (6 of 19) treated with rucaparib. The ORR (including confirmed and unconfirmed responses) was 16% (3 of 19). The duration of confirmed responses was 36 and 49 weeks (both ongoing), the response in the third patient was not confirmed.

Cancer patients harboring BRCA mutations who do not respond to platinum based chemotherapy display decreased sensitivity to PARP inhibitors. For this reason, platinum-refractory patients are excluded from enrollment. In particular, pancreatic cancer patients who have progressed within 6 months of starting previous platinum-based chemotherapy are not eligible.[46]

1.2.4. Study Rationale

Based on the mechanisms of action discussed in Sections 1.1.1 and 1.1.2, talazoparib and avelumab 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.

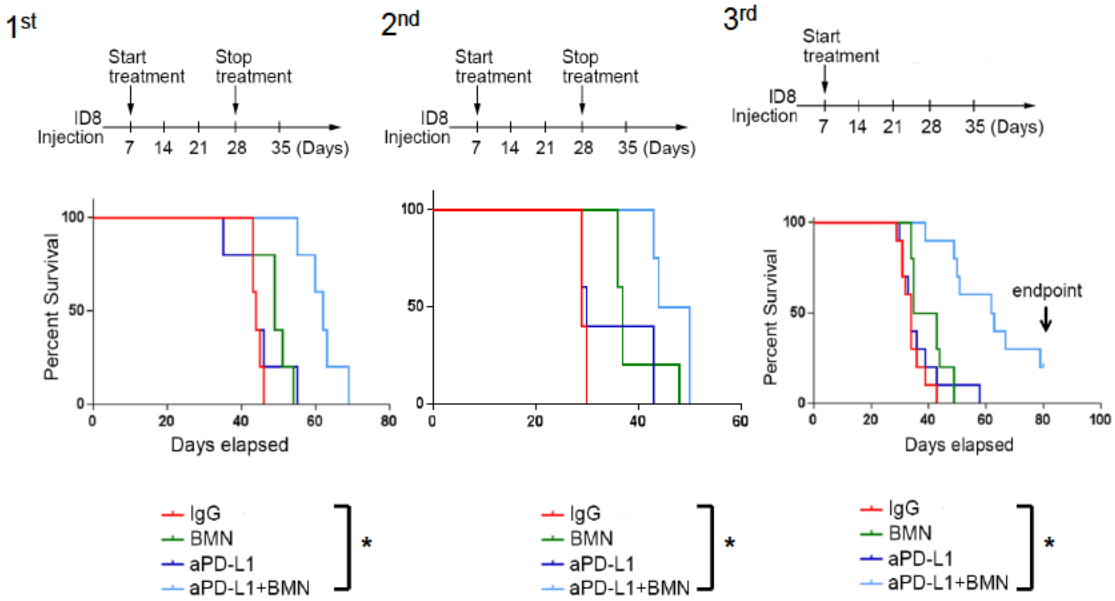
Specifically, the activity of avelumab depends on generation of a productive immune response, composed of effective antigen presentation, T-cell priming, infiltration of tumors, and recognition and killing of tumor cells.[49] Talazoparib, via its ability to promote increased DNA damage, has the potential 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),[13] and the second being activation of the STING pathway via generation and detection of cytosolic DNA.[14,15] 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.[51] Finally, DNA damage has been shown to lead to up-regulation of MHC, NKG2DL, and ICOSL,[16,17] 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 [redacted] and to promote T cell and NK cell infiltration and activation in a mouse model of ovarian cancer.[18]

[redacted]

However, talazoparib treatment has also been shown to lead to 2-3 fold increased expression of PD-L1 by tumor cells,[20] suggesting that this may represent a mechanism of resistance to possible talazoparib-mediated anti-tumor immunity, and suggesting 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 (Figure 2) 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.

Figure 2. Combination of Talazoparib (BMN 673) and Anti-mouse PD-L1 Treatment Significantly Prolongs Survival in an Ovarian Cancer Model



Survival curves from 3 independent experiments comparing the combination of BMN 673 (0.33 mg/kg daily by oral gavage) and anti-PD-L1 (200 µg/mouse every 3 days) to talazoparib alone, anti-PD-L1 alone, or IgG control. In the left and middle panels, mice were treated for 3 weeks and treatment was stopped to monitor survival of the mice. In the right panel, mice were treated continuously until the mice met criteria for euthanasia and survival was monitored. Statistical analysis was conducted by log rank test. The combination treatment significantly improved mouse survival compared to IgG control in three experiments ($p < 0.01$).[40]

Given the proposed mechanism of the avelumab and talazoparib combination, one subgroup of patients likely to benefit most from the combination will be those whose tumors are most sensitive to talazoparib mediated DNA damage. Clinical and preclinical studies have indicated that such sensitivity is increased in tumors with defective repair of double strand DNA breaks (DSBs).[41] One underlying reason for defective DSB repair is the presence of mutations in key genes, either at the germline or somatic level. The BRCA1, BRCA2 and ATM genes are three of the best evidenced examples of such genes and have been associated with increased response, or improved outcome, following treatment with a number of PARP inhibitors including olaparib, rucaparib, and niraparib.[42,43,44,54] Analysis of publicly available data within The Cancer Genome Atlas (TCGA),[56] indicates presence of mutations in BRCA 1/2 and ATM occur with variable frequency across many tumor types, with an average prevalence across solid tumors of 7.7%. It is expected that all tumors with such defects will present with increased sensitivity to talazoparib mediated DNA damage, and therefore have the potential to benefit from the combination of talazoparib and avelumab.

It is important to note that, since avelumab is an immunoglobulin (Ig)G1 mAb eliminated by intracellular lysosomal proteolytic degradation throughout the entire body while talazoparib is a small molecule cleared primarily via excretion of unchanged parent drug and metabolized to a minor extent via oxidation and dehydrogenation, no PK DDI is anticipated between avelumab and talazoparib when given in combination.

In conclusion, considering the above described mechanism of action and the preliminary clinical activity observed for the investigational products or one agent of the same class (see Section 1.2.1.1, Section 1.2.2.2, and Section 1.2.3), the avelumab and talazoparib combination is proposed for evaluation in patients with locally advanced (primary or recurrent) or metastatic solid tumors with a BRCA1, BRCA2, or ATM gene defect (based on local assessment of germline or tumor DNA) who have received at least 1 line of SOC treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified.

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 FDA as the first treatment for mMCC.[5] Avelumab was originally dosed on a mg/kg basis in order to reduce inter-patient 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.[59,60,61] 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 patients 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, 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. Flat dosing for avelumab of 800 mg Q2W has recently been approved in the US for the Merkel Cell Carcinoma (MCC) and UC indications [avelumab United States Package Insert (USPI), October 19, 2018].

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.

1.2.5.2. Talazoparib

The dose levels of talazoparib to be evaluated in this study are supported by clinical studies in patients with advanced malignancies. In the PRP-001 Phase 1 study in patients with advanced or recurrent solid tumors, talazoparib was escalated from 0.025 to 1.1 mg QD and the recommended dose for further development was determined to be 1 mg QD. Data from this study at 1 mg/day demonstrated objective responses or clinical benefit (CR, PR, or stable

disease ≥24 weeks) in patients with breast, ovarian/peritoneal, pancreatic cancer, SCLC, and Ewing sarcoma. The dose level of 1 mg QD was selected for the randomized Phase 3 study 673-301 in patients with BRCA 1/2 mutations and locally advanced or metastatic breast cancer.

Recommended Phase 2 Dose

For this present study, the dose level of talazoparib 1 mg orally (PO) QD in combination with avelumab 800 mg IV Q2W was selected following evaluation of 12 patients after 1 cycle of treatment in the Phase 1b portion of Study B9991025, a Phase 1b/2 study in patients with advanced solid tumors. As of the 18 May 2018 data cutoff date, the most frequently reported TEAEs were anemia (8 patients, 66.7%), neutropenia (7 patients, 58.3%), and chills and thrombocytopenia (both 5 patients, 41.7%). The most frequently reported Grade 3 TEAEs were thrombocytopenia (4 patients, 33.3%), anemia (3 patients 25.0%), and neutropenia (2 patients, 16.7%); a serious AE (SAE) of anemia was reported in 1 patient (8.3%). There were no Grade 4 TEAEs. No AEs leading to treatment discontinuation of any of the study drugs was reported. Seven (7) patients (58.3%) experienced AEs that led to interruption of avelumab [thrombocytopenia (5 patients, 41.7%), anemia and neutropenia (both 2 patients, 16.7%); chills and fatigue (both 1 patient, 8.3%), and restlessness (1 patient, 8.3%)] and eight (8) patients (66.7%) experienced AEs that led to interruption of talazoparib [thrombocytopenia (5 patients, 41.7%), anemia and neutropenia (both 3 patients, 25%), and fatigue (1 patient, 8.3%)]. Three (3) patients (25.0%) experienced TEAEs which led to talazoparib dose reduction and were declared to be DLTs: thrombocytopenia led to talazoparib dose reduction to 0.75 mg QD; of these, one patient required further dose reduction to 0.5 mg QD. A third patient experienced thrombocytopenia and anemia together, leading to a talazoparib dose reduction to 0.75 mg. As the frequency of the TEAEs were generally consistent with the frequency of TEAEs following administration of the single agents and were determined to be generally manageable, the Recommended Phase 2 Dose (RP2D) for talazoparib in combination with avelumab at 800 mg IV Q2W was established at 1 mg PO QD. The starting dose of talazoparib for patients with moderate renal impairment (CL_{CR} = 30-59 mL/min) will be 0.75 mg PO QD to account for the lower talazoparib clearance.

Although no PK drug-drug interaction is expected between avelumab and talazoparib, concentration-time data will be measured on this study for both avelumab and talazoparib following coadministration at single dose and at steady state, and will be compared with historical PK data for avelumab and talazoparib as single agents.

1.2.6. 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 1.2.1 and Table 3. 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 1.2.1. 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 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 avelumab infusions (Cycles 1-2) and as clinically indicated thereafter.

Talazoparib has also demonstrated single-agent clinical activity in patients with advanced solid tumors with DNA repair pathway abnormalities, particularly those associated with BRCA 1/2 and PTEN dysfunction, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001, as described in Section 1.2.2. Also, in an ongoing Phase 3, open-label, randomized, parallel-group study, (N=431, randomized 2:1 on talazoparib vs chemotherapy) in patients with locally advanced or metastatic breast cancer with germline BRCA 1/2 mutations, talazoparib monotherapy demonstrated longer PFS and better ORR than standard of care chemotherapy (median PFS: 8.6 months vs 5.6 months, HR: 0.54, 95% CI: 0.41- 0.71, p<0.0001; ORR: 62.6% vs 27.2%; odds ratio: 4.99, 95% CI: 2.9-8.8, p<0.0001; per RECIST 1.1, confirmation of CR/PR was not required).[24]

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 severity and typically resolved with temporary dose interruptions or reductions.[23] In the EMBRACA study, the most common AEs observed with talazoparib (>20%, all grade) 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 serious AEs 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.[24]Preliminary safety data from B9991025 with talazoparib combined with avelumab has been found to be generally consistent with the safety profiles from the single agents. The avelumab plus talazoparib combination is anticipated to improve the anti-tumor activity of each drug when given as single-agent, while maintaining the manageable safety profiles of avelumab and talazoparib administered as single agents.

The expected low incidence of 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 solid tumors with BRCA 1/2 or ATM gene defects.

1.2.7. Rationale for Biomarker Assessments and Prospective Patient Selection

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 optimally effective in patients that have greater sensitivity to talazoparib-mediated DNA damage. This study will enroll patients expected to have such increased sensitivity, based on historic evidence of germline or somatic defects in BRCA1, BRCA2 or ATM, which have been associated in a number of studies with increased sensitivity to PARP inhibitors.[43,44,54]

In order to allow for confirmation of historic BRCA 1/2 and ATM test results, all patients entering the study are required to provide tumor tissue, in the form of a minimum of 15 slides, for central testing.

A number of assessments will also be undertaken in tumor tissue in order to understand the immune context of patient tumors, which will likely also be a key contributing factor in response to the combination of talazoparib and avelumab. One key assessment of interest is PD-L1 expression by tumor and/or immune cell types in the tumor, measured by immunohistochemistry. While initial studies have not indicated a relationship between PD-L1 expression and response to PARP inhibitor combinations with anti-PD-1/PD-L1 antibodies, these studies were small in nature and PD-L1 has shown utility as a potential predictive marker across multiple tumor types treated with anti-PD-1/PD-L1 antibodies.[25,55] Additional assessments may include, but are not limited to, assessment of infiltrating immune cell number and phenotype by immunohistochemistry or immunofluorescence, relative expression of genes representative of immune activation versus suppression by gene expression profiling, the number and diversity of T-cell receptor (TCR) sequences by DNA sequencing, and assessment of mutational or neoantigen load within tumors. To enable the above mentioned biomarker assessments, the provision of a pretreatment tumor tissue sample is mandatory (see Section 7.4.1.1); also, tumor tissue is requested for patients who undergo tumor biopsy or resection as part of routine clinical care during the study period, and every effort should be made to obtain end of treatment biopsies (see Section 7.4.1.2).

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 points. Circulating tumor (ct)DNA will be collected from all patients at baseline, and will be used to correlate the presence defects in BRCA 1/2 and ATM in ctDNA with those in tissue, in order to determine the feasibility of a blood based biopsy approach for future patient selection. In addition ctDNA samples collected during and at the end of treatment will be used to assess changes in the presence of such defects, and defects in other genes, which may inform the mechanism and timing of resistance to therapy. Samples of serum, plasma, RNA and DNA from blood will be used to assess a number of potential pharmacodynamic, predictive and resistance biomarkers including, but are not limited to, gene expression profiling, diversity of TCR sequences, and proteomic signatures.

In the event that clinical benefit is not observed or is transient, an understanding of the mechanisms of resistance may help guide optimal patient selection for future development of the combination. For these reasons, tumor biopsies performed at the End of Treatment visit or in the event of permanent treatment discontinuation due to disease progression, are requested from patients, unless clinically contraindicated. If the sponsor considers sufficient data have been obtained to confirm possible causes for lack of clinical benefit, collection of tumor tissue from End of Treatment tumor biopsies may be discontinued.

1.2.8. Banked Biospecimen Collection Rationale

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

Banked biospecimens retained in the BBS also can be used in research on solid tumors.

Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	**Primary Endpoint:**
• To evaluate ORR of avelumab in combination with talazoparib, in patients with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.	• Confirmed OR in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by Blinded Independent Central Review (BICR), using RECIST v1.1 (Appendix 3) and, in patients with mCRPC, RECIST v1.1 and PCWG3 (bone) (Appendix 4).
Secondary Objectives:	**Secondary Endpoints:**
• To assess the overall safety and tolerability of avelumab in combination with talazoparib. • To characterize the PK of avelumab and talazoparib when given in combination. • To evaluate the immunogenicity of avelumab when given in combination with talazoparib. • To assess other measures of the anti-tumor activity of avelumab in combination with talazoparib. • To assess the correlation of anti-tumor activity of avelumab in combination with talazoparib with PD-L1 expression in baseline tumor tissue.	• Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing. • PK parameters including: pre-dose/trough concentrations (C_{trough}) for avelumab and talazoparib, post-dose concentrations for talazoparib, and maximum concentrations (C_{max}) for avelumab.

• To assess the correlation of anti-tumor activity and emergence of resistance with defects in a panel of key oncogenes, including BRCA1/2 and ATM, and TMB in circulating tumor DNA (ctDNA) and tumor tissue at baseline, during treatment and at the end of treatment.	• Avelumab anti-drug antibody (ADA) levels and neutralizing antibodies (Nab) against avelumab. • Confirmed OR as assessed by the investigator, using RECIST v1.1 (Appendix 3) and, in patients with mCRPC, RECIST v1.1 and PCWG3 (Appendix 4). • Time to event endpoints: Endpoints as assessed by BICR and as assessed by the investigator, using RECIST v1.1 (Appendix 3) and in patients with mCRPC, RECIST v1.1 and PCWG3 (Appendix 4), including time to tumor response (TTR), duration of response (DR), and progression free survival (PFS). Additional time-to-event endpoints include overall survival (OS) for all patients and time to prostate-specific antigen (PSA) progression (≥25% increase) for mCRPC patients. • PSA response ≥50% decrease and CTC count conversion for patients with mCRPC. • Cancer antigen (CA)-125 response ≥50% decrease for patients with ovarian cancer. • PD-L1 expression level in baseline tumor tissue. • Presence of defects in a panel of key oncogenes, including BRCA 1/2 and ATM, and TMB in ctDNA and tumor tissue at baseline, during treatment, and at the end of treatment.
[redacted]	[redacted]

	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This is a Phase 2b, open-label, multi-center, non-randomized study of avelumab in combination with talazoparib in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or loss-of-function somatic BRCA1 or BRCA2, or ATM gene defect, as determined by local assessment and classification, who have received at least 1 line of SOC treatment for locally advanced or metastatic disease unless prior treatment requirements are otherwise specified. Two cohorts will be enrolled in parallel:

- Cohort 1 will enroll up to approximately 150 patients with locally advanced or metastatic solid tumors with one or more defects in the BRCA1 or BRCA2 genes;
- Cohort 2 will enroll up to approximately 50 patients with locally advanced or metastatic solid tumors with one or more defects in the ATM gene.

  Note: in the event that a patient has concomitant defects in more than 1 of the three genes (BRCA1 or BRCA2 or ATM), they will be enrolled in Cohort 1.

Patients will continue on the study treatment until disease progression or withdrawal from study treatment for other reasons. See Section 6.3 for reasons for withdrawal from the study treatment or the study follow-up.

4. PATIENT ELIGIBILITY CRITERIA

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

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team. To confirm that participants meet critical eligibility criteria, sites may be asked to complete a Patient Enrollment Verification Form for review and confirmation by the sponsor prior to enrollment.

4.1. Inclusion Criteria

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

1. Pathogenic or likely pathogenic germline or somatic gene defect as determined by local assessment and classification:

- One or more BRCA1 or BRCA2 gene defect (Cohort 1);

- ATM gene defect in the absence of concurrent BRCA 1/2 defect (Cohort 2).

  Note: in the event that a patient has concomitant defects in more than 1 of the three genes (BRCA1 or BRCA2 or ATM), they will be enrolled in Cohort 1.

The presence of gene defects must have been determined by local assessment and classification using a test of either germline or tumor DNA which was performed in a CAP/CLIA-certified (or comparable local or regional certification) laboratory.

2. Histological diagnosis of locally advanced (primary or recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent, as follows:

   a. Recurrent Epithelial Ovarian Cancer:

      - Patients must have received at least 1 but no more than 5 total prior cytotoxic chemotherapy regimens, including at least 1 course of platinum-based therapy;

      - Patients must not have progressed during or within 1 month after the last dose of the most recent platinum-based chemotherapy;

      - Platinum sensitivity requirements:

        - If previously treated with ≤2 prior cytotoxic chemotherapy regimens, patients must have had disease progression within 6 months after the last dose of platinum-based chemotherapy, also termed “platinum-resistant recurrent disease”;

        - If previously treated with >2 prior cytotoxic chemotherapy regimens, platinum-sensitive recurrent disease is allowed.

      - Any treatment regimen that began with cytotoxic chemotherapy and continued with another regimen for maintenance therapy following best response to initial cytotoxic regimen will count as one line of prior therapy.

   b. TNBC (defined as ER- and PgR-negative [IHC nuclear staining <5%] and HER2-negative [IHC 0, 1+, or 2+ and/or ISH non-amplified with ratio less than 2.0]) or hormone-receptor-positive (HR+), HER2-negative breast cancer:

      - Have been previously treated with no more than 3 prior chemotherapy regimens for locally advanced or metastatic breast cancer;

      - There is no limit on the number of prior endocrine therapies or targeted anti-cancer therapies such as mammalian target of rapamycin (mTOR) or cyclin-dependent kinase (CDK)4/6 inhibitors, or vascular endothelial growth factor inhibitors (VEGF);

- Previous neo-adjuvant/adjuvant treatment counts as 1 line of prior chemotherapy if disease progression occurred while on treatment or within 6 months after the last treatment dose;

- Patients must have received treatment with a taxane- or anthracycline-containing chemotherapy regimen in the neo-adjuvant, adjuvant, or advanced setting, unless deemed unsuitable for these treatments;

- Patients that have previously been treated with platinum-based chemotherapy in the neo-adjuvant/adjuvant setting must not have had disease progression while on treatment or within 6 months after the last dose of platinum-based chemotherapy;

- Patients that have previously been treated with platinum-based chemotherapy in the advanced/metastatic setting must not have had disease progression within 6 months of initiation of a platinum-containing regimen;

- Patients with HR+ breast cancer must have received at least 1 prior endocrine therapy (adjuvant or metastatic), unless deemed not suitable for endocrine therapy.

c. Metastatic castration-resistant prostate cancer (mCRPC) without small cell features:

- Patients with disease spread limited to regional pelvic lymph nodes (below the aortic bifurcation) are not eligible unless bone metastasis is present on bone scan;

- Progressed on at least 1 line of second-generation anti-androgen therapy (enzalutamide and/or abiraterone acetate/prednisone) for treatment of mCRPC;

- Have received no more than 2 prior chemotherapy regimens for mCRPC. Patients may have received radium-223, which does not count for a line of prior chemotherapy regimen;

- Serum testosterone ≤1.73 nmol/L (50 ng/dL);

- Bilateral orchiectomy or ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) agonist/antagonist (surgical or medical castration);

- Progressive disease at enrollment defined as 1 or more of the following 3 criteria:
  - A minimum of 3 consecutive rising PSA values with an interval of at least 1 week between determinations. The screening PSA value must be ≥2 µg/L (2 ng/mL) if qualifying solely by PSA progression;
  - Disease progression as defined by RECIST v1.1;
  - Bone disease progression defined by Prostate Cancer Working Group 3 (PCWG3) with 2 or more new metastatic lesions on bone scan (confirm ambiguous results by other imaging modalities).

d. Metastatic ductal adenocarcinoma of the pancreas:

- Have been previously treated with at least 1 but no more than 2 prior cytotoxic chemotherapy regimens (including at least one of the following: FOLFIRINOX or a gemcitabine-containing regimen) unless deemed unsuitable or patient declined these therapies;
- Patients must not have had disease progression within 6 months of initiation of a platinum-containing regimen.

e. Any other advanced solid tumor:

- Have received at least 1 prior SOC regimen, if it exists, as appropriate for the respective tumor type unless deemed unsuitable, or declined these therapies;
- Patients must not have had disease progression within 6 months of initiation of a platinum-containing regimen;
- Patients with NSCLC harboring B-Raf proto-oncogene (BRAF)^{V600} mutations or ALK and c-Ros oncogene 1 (ROS1) translocations/rearrangements must have received the appropriate targeted therapy as approved by the relevant health care authority. Patients with activating EGFR mutations are not eligible; non-squamous cell histologies require testing if EGFR status is unknown.

3. Availability of a fresh or recent tumor tissue sample from a diagnostic biopsy/surgery or a metastatic tumor biopsy; the sample must have been obtained within 24 months prior to study enrollment. When only bone disease is present, an archival tumor tissue sample obtained within 5 years prior to study enrollment may be accepted for non-prostate cancer patients and a fresh bone biopsy may be accepted for prostate cancer patients only). (See Section 7.4.1 for details).

4. Have progressive disease at study enrollment as defined by RECIST v1.1 (except for mCRPC, who must meet criterion 2c above).

5. Must have measurable disease by RECIST v1.1 with at least 1 measurable lesion that has not been previously irradiated (patients with mCRPC may have only non-measurable disease).

6. Age ≥18 years (except in Japan, where patients must be ≥20 years old).

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

8. Adequate bone marrow function (without hematopoietic growth factor or transfusion support within 14 days prior to study enrollment), including:

   a. Absolute Neutrophil Count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L.

   b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L.

   c. Hemoglobin ≥9 g/dL (≥5.6 mmol/L).

9. Adequate renal function defined by an estimated creatinine clearance ≥30 mL/min according to the Cockcroft-Gault formula as:

   - CL_{CR}={[(140–age) × weight)]/(72 x S_{CR})} × 0.85 (if female), where CL_{CR} (creatinine clearance) is measured in mL/min, age is expressed in years, weight in kilograms (kg), and S_{CR} (serum creatinine) in mg/dL;

   - Or as measured by 24h urine assessment.

     NOTE: Patients with moderate renal impairment (30-59 mL/min) will receive a reduced starting dose for talazoparib (See Section 5.4.2).

10. Adequate liver function, including:

    a. Total serum bilirubin ≤1.5 × the upper limit of normal range (ULN);

    b. Aspartate and Alanine aminotransferase (AST and ALT) ≤2.5 x ULN.

11. Female patients of childbearing potential must have negative serum pregnancy or urine pregnancy test at screening.

    Women in the following categories are <u>not</u> considered to be women of child-bearing potential (WOCBP):

    1. Premenopausal female with 1 of the following:

       - Documented hysterectomy;

       - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

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

4.2. Exclusion Criteria

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

1. Prior treatment with a PARP inhibitor.

2. Prior immunotherapy with anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody.

3. Prior anti-cancer therapy within 2 weeks prior to study enrollment or prior radiation therapy within 2 weeks prior to study enrollment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed at least 2 days prior to study enrollment and no clinically significant toxicities are expected (eg, mucositis, esophagitis).

4. Major surgery within 4 weeks prior to study enrollment.

5. Current use of immunosuppressive medication at the time of study enrollment, EXCEPT for the following permitted steroids:

    a. Intranasal, inhaled, topical steroids, eye drops or local steroid injection (eg, intra-articular injection);

    b. Systemic corticosteroids at physiological doses ≤10 mg/day of prednisone or equivalent;

    c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).

6. Known prior severe hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03 Grade ≥3).

7. Known history of immune-mediated colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis.

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

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

10. Administration of live attenuated vaccines within 4 weeks of study enrollment.

11. Diagnosis of myelodysplastic syndrome (MDS).

12. 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.

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

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

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

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

17. Active infection requiring systemic therapy. Minor infections, eg, periodontal or urinary tract infection (UTI) infection, which may be treated with short term oral antibiotics are allowed.

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

19. Current or anticipated use of strong P-gp inhibitors within 7 days prior to enrollment, or anticipated use during the study. For a list of strong P-gp inhibitors, refer to Section 5.7.10.

20. Inability to swallow capsules, known intolerance to talazoparib or its excipients, known malabsorption syndrome, or other condition that may impair absorption of talazoparib.

21. Bisphosphonate or denosumab dosage that was not stable (ie, not the same) for at least 2 weeks before study enrollment for patients receiving these therapies.

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

23. Diagnosis of any other malignancy within 2 years prior to study enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast, bladder, or cervix, or low-grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (eg, surgery, radiation, or castration), or other early-stage low-risk cancers.

24. Pregnant female patients, breastfeeding female patients, and female patients of childbearing potential who are unwilling or unable to use a method of highly effective contraception as outlined in this protocol during treatment and for at least 30 days after the last dose of avelumab and for at least 7 months after the last dose of talazoparib; fertile male patients with female partners of reproductive potential or pregnant partners, unwilling to use a condom (even after vasectomy) during treatment and for at least 4 months after the last dose of talazoparib.

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

4.3. Lifestyle Requirements

In this study, all patients will receive avelumab for which the teratogenic risk is currently unknown, in combination with talazoparib, which has been associated with genotoxic and teratogenic risk.

All female patients who are of childbearing potential, who are, in the opinion of the investigator, sexually active and at risk for pregnancy must agree to use highly effective contraception, preferably with low user dependency, during treatment and for at least 30 days after the last dose of avelumab and at least 7 months after the last dose of talazoparib.

Fertile male patients with female partners of reproductive potential or pregnant partners, must agree to use a condom (even after vasectomy) during treatment and for at least 4 months after the last dose of talazoparib. Female partners of reproductive potential should use an additional highly effective contraceptive method for at least 4 months after the patient's last dose of talazoparib.

The investigator or his or her designee, in consultation with the patient, will confirm that the patient has selected an appropriate method of contraception for the individual patient and his/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 highly effective contraception consistently and correctly and document the conversation, and the patient's affirmation, in the patient's chart (patients need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the patient or partner.

CONTRACEPTIVES ALLOWED DURING THE TRIAL INCLUDE:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - oral;
    - intravaginal;
    - transdermal;
    - injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - oral;
    - injectable.

3. Sexual abstinence:

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

4.4. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and

the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council for 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.

5.1. Allocation to Treatment

All patients will be assigned to receive a fixed dose of avelumab 800 mg Q2W intravenously and oral talazoparib at 1 mg QD or 0.75 mg QD for patients with moderate renal impairment.

Assignment of patient number, patient enrollment, and allocation of study treatment will be managed by an Interactive Response Technology (IRT) system. At the time that a patient has signed informed consent and entered screening, the site should contact the IRT system to obtain the patient identification number. Once a patient has met all eligibility criteria, the site then contacts the IRT system to enroll the patient and to obtain the study treatment allocation information. Study treatment must be initiated preferably on the day of enrollment, but no later than 3 days after enrollment.

At the time of enrollment, site personnel (study coordinator or specified designee) will be required to enter into or select information from the IRT system including but not limited to the user's identification (ID) and password, the protocol number, the patient number, and the date of birth of the patient. The IRT system will then provide a treatment assignment and dispensable unit (DU) or vial number. The IRT system will also provide a confirmation report containing the patient number and DU or vial 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.

5.2. Patient Compliance

The information related to each trial drug administration will be recorded in the case report form (CRF) as detailed below. 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. Avelumab Patient Compliance

All doses of avelumab will be administered at the investigator site by well-trained medical staff. The total dose and start and stop times of the avelumab infusion, including infusion rate as well as start and stop times of any interruptions to infusions and/or changes in rate of infusion, will 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, including date of preparation, patient identification number, total dose and volume prepared, date and time of expiry, and the initials of clinical site personnel preparing and approving the infusion. 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 avelumab within a given cycle for non-medical reasons. If 1 infusion is missed and the interval between the subsequent infusion and the last administered treatment is longer than 4 weeks for non-medical reasons, this would also be considered as noncompliance.

5.2.2. Talazoparib Patient Compliance

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 will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed talazoparib doses. The time of talazoparib dose administration and the total dose of talazoparib taken each day will be recorded in the dosing diary. Patients will be required to return the completed patient dosing diary for talazoparib on Day 1 of every cycle for timely review by site personnel and discussion of missed doses and/or compliance issues to ensure accurate data entry for the Dosing CRF.

On days when the patient's talazoparib dose is given at the clinic due to 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.

Patients will be considered out of compliance if ≥20% of the expected monthly doses are missed within a given cycle for non-medical reasons.

5.3. Investigational Product Supplies

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

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

Avelumab will be packed in boxes each containing 1 vial.

Avelumab will be shipped and must be stored under refrigerated conditions (2°C to 8°C) that are monitored with temperature control monitoring devices.

5.3.1.2. Talazoparib

Talazoparib will be provided as capsules for oral administration. The 0.25 mg (opaque white, size 4) and 1.0 mg (opaque pale-pink, size 4) capsules will be supplied in separate bottles and labeled according to local regulatory requirements. Talazoparib is packaged in induction sealed, high-density polyethylene bottles with child-resistant caps with 30 capsules of a single strength per bottle. Storage temperature is 15°C to 30°C. Schedule of patient visits must take into account number of talazoparib capsules dispensed, to ensure that patient has sufficient quantity of drug supply.

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. Avelumab

See the IP manual for instructions on how to prepare avelumab 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.

For administration in this trial, 4 vials of avelumab drug product must be diluted with 0.9% saline solution (sodium chloride). Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Investigational Product Manual.

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

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.

5.3.2.2. 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 of 30 capsules per bottle. 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 every 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.[76] Patients should be advised that oral anti-cancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

5.4. Administration

5.4.1. Combination Therapy Administration

On Days 1 and 15 of each cycle, when both avelumab and talazoparib are administered at the investigator site, the following must occur in the order specified:

1. All required tests and assessments will be performed, as per the Section 7 and blood will be drawn for PK and ADA assessments (when scheduled);

2. Avelumab premedication, as described below in Section 5.4.3, and talazoparib will be administered to the patient in any order chosen by the qualified site personnel;

3. Avelumab infusion will start within 30-60 minutes after the avelumab premedication was administered and after dosing with talazoparib;

4. Blood will be drawn for PK assessments (when scheduled) immediately at the end of the avelumab infusion and the patient will remain in the clinic for observation for at least 30 minutes after the avelumab infusion.

Treatment with avelumab and talazoparib will continue until disease progression is confirmed by the investigator (except where treatment is allowed beyond progression, as per Section 5.4.7), patient refusal, unacceptable toxicity, or until the study is terminated by the sponsor, whichever occurs first.

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

5.4.2. Talazoparib Administration

Talazoparib 1 mg will be taken QD orally, starting on Cycle 1 Day 1 (C1D1), and treatment should continue until End of Treatment.

For patients with moderate renal impairment (CL_{CR} = 30-59 mL/min), the talazoparib starting dose should be reduced to 0.75 mg QD. Measurement of CL_{CR} will be repeated for patients whose degree of renal impairment changes between screening and enrollment, if this change is suspected to be due to the hydration status of the patient, to determine the exact starting dose of talazoparib before initiation of study treatment.

On Days 1 and 15 of each 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 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 them 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 forgets his/her daily dose of talazoparib at the time typically taken, but remembers this on the same day, within 12 hours of the usual dose time, the dose may be taken at that time. Any dose that is missed (not taken within 12 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day. Patients should not make up vomited doses; dosing should resume on the next calendar day unless otherwise instructed.

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.

5.4.3. Avelumab Premedication

In order to mitigate infusion-related reactions, patients have to be premedicated with an antihistamine and with paracetamol (acetaminophen) 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 at least 30 minutes after the avelumab premedication was administered.

5.4.4. Avelumab Administration

Avelumab will be administered at 800 mg as a 1-hour IV infusion starting 30-60 minutes after the mandatory premedication was administered, as per Section 5.4.3, at the investigator site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Investigator sites should make every effort to target the timing of the avelumab infusion to be as close to 1 hour as possible. The exact duration of infusion should be recorded in both the source documents and the CRFs. Additionally, the start and stop times of any interruptions to infusion and/or changes in rate of avelumab infusion will also need to be recorded in source documents. After Cycle 1, avelumab may be administered up to 3 days before or after the scheduled treatment day of each cycle for administrative reasons.

5.4.4.1. Special Precautions for Avelumab Administration

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

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 Table 6. Patients should be instructed to immediately report to the investigator any delayed reactions that may occur after they leave the clinic.

5.4.5. Food Requirements

Both investigational products may be administered without regard to food.

5.4.6. Recommended Dose Modifications

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.

Treatment/dose modifications may occur independently for each investigational product in the combination based on the observed toxicity and 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.

See Section 5.4.6.3 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.

5.4.6.1. Dosing Interruptions

Guidelines for study treatment modifications for patients experiencing adverse events are provided in Sections 5.4.6.3, 5.4.6.4, and 5.4.6.5.

Doses of either investigational product that were omitted for toxicity are not replaced within the same cycle. The need for a dose reduction for talazoparib at the time of treatment resumption should be based on the criteria defined in Section 5.4.6.3.

Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the investigator.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) for >7 consecutive days, treatment resumption will be decided in consultation with the sponsor.

5.4.6.2. Dose Reductions of 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 in Section 5.4.6.3. 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 (see Table 4 below for the available dose levels).

The talazoparib starting dose level for the present study is 1 mg QD.

Doses less than 0.5 mg are not permitted. Patients unable to tolerate 0.5 mg QD, will be permanently discontinued from the talazoparib, but may continue on single agent avelumab. Available dose levels for dose reductions are listed below.

Table 4. Dose Levels for Dose Reductions of Talazoparib

Dose Level	Talazoparib Dose (Oral)
D0	1 mg QD
D-1	0.75 mg QD
D-2	0.5 mg QD [a]

[a] Talazoparib dose de-escalation below 0.5 mg QD is not allowed.
D = dose; QD = once daily

Once a dose has been reduced due to toxicity 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.

If a dose reduction is required, the patient may need to return to the clinic to receive new drug supply prior to the next scheduled visit since dosage strengths of the capsules may be different. Site personnel must ensure the patients are instructed how to take the reduced dose and that the patients have the correct dosage strength for the reduced dose.

Recommended dose reductions for talazoparib are described in Section 5.4.6.3.

5.4.6.3. Study Treatment Modifications for Avelumab and Talazoparib Drug-Related Toxicity (excluding infusion-related reactions and immune-related adverse events)

Recommended avelumab and talazoparib treatment modifications 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 5.4.6.4.

For patients receiving avelumab, either as a single agent or in combination with talazoparib, any AE suspected to be immune-related should be managed according to the guidance for management of irAEs in Section 5.4.6.5.

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 monitor weekly until resolve to baseline. • Talazoparib may be reduced by 1 dose level, per Section 5.4.6.2. • Permanently discontinue if persists for >4 weeks without recovery to baseline. Refer to hematologist for evaluation including assessment of possible MDS/AML.	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 (hemoglobin >10 g/dL) 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).

• **Neutropenia Grade ≥3** (ANC <1000/μL)	• Hold talazoparib and monitor weekly until ANC ≥1500/μL.
	• Resume talazoparib based on the following recovery times:
	  ◦ ≤1 week: No change;
	  ◦ >1 week: Talazoparib may be reduced by 1 dose level, per Section 5.4.6.2.
	• Permanently discontinue talazoparib if persists for >4 weeks without recovery to ANC ≥1500/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.
		• 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).

• **Thrombocytopenia Grade ≥3** (platelets <50,000/μL)	• Hold talazoparib and monitor weekly until platelets ≥75,000/μL.
	• Resume talazoparib based on the following recovery times:
	  ◦ ≤1 week: No change;
	  ◦ >1 week: Talazoparib may be reduced by 1 dose level, per Section 5.4.6.2.
	• Permanently discontinue talazoparib if persists for >4 weeks without recovery to platelets ≥75,000/μL. Refer to hematologist for evaluation including assessment of possible MDS/AML.
		• Hold avelumab.
		• Re-initiate avelumab once toxicity Grade ≤1 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
Non-hematologic toxicities		
Grade 1	• No requirement for dose interruption or dose reduction.	• Continue as per schedule. • For suspected immune-related toxicities due to avelumab follow guidance in Section 5.4.6.5.
Grade 2	• For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 5.4.6.5, 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 5.4.6.5.

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

	Talazoparib	Avelumab

Grade 3	• Hold talazoparib.
	• Resume talazoparib reduced by 1 dose level, per Section 5.4.6.2 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 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 5.4.6.5, talazoparib should also be placed on hold until toxicity is Grade ≤1 or baseline.
		• 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 5.4.6.5.

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

	Talazoparib	Avelumab

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 5.4.6.5.

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

5.4.6.4. 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]
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 patient. • 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. Prophylactic corticosteroids are not permitted.

5.4.6.5. Immune-Related Adverse Events Toxicity Management

For patients receiving avelumab, either as a single agent or 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)	**Initial Management**	**Follow-up Management**
Grade 1 • **Diarrhea:** <4 stools/day over Baseline. • **Colitis:** asymptomatic.	• Continue avelumab therapy. • Symptomatic treatment (eg, loperamide).	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately. • If worsens, treat as Grade 2, 3 or 4.
Grade 2 • **Diarrhea:** 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL. • **Colitis:** abdominal pain; blood in stool.	• Withhold avelumab therapy. • Symptomatic treatment.	• If improves to Grade ≤1, resume avelumab therapy. • If persists >5-7 days or recurs, treat as Grade 3 or 4.

Table 7. Management of Immune-Related Adverse Events

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*
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤30% body surface area.	• Continue avelumab therapy. • Symptomatic therapy (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).

Table 7. Management of Immune-Related Adverse Events

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	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 opportunistic infections. • Consider bronchoscopy, lung biopsy.	• Re-assess every 1 to 3 days. • When symptoms return to Grade ≤1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids 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)	**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.

Table 7. Management of Immune-Related Adverse Events

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.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**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. • Add prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • Nephrology consultation.	• If returns to Grade ≤1, taper steroids over at least 1 month.

Table 7. Management of Immune-Related Adverse Events

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 equivalent. • Add prophylactic antibiotics for opportunistic infections.	• Once improving, taper steroids over at least 1 month. • If no improvement or worsening, consider additional immunosuppressants (eg, azathioprine, cyclosporine A).
*Local guidelines, or eg, ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	**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	• Withhold avelumab therapy. • Consider hospitalization. • Endocrinology consult.	• Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without

Table 7. Management of Immune-Related Adverse Events

insufficiency, type I diabetes mellitus).	• 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).	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 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.	• Resume avelumab once symptoms and hormone tests improve to Grade ≤1 (with or without hormone replacement). • In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. • Continue hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
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.

Table 7. Management of Immune-Related Adverse Events

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 longer.**	• Permanently discontinue avelumab therapy. • Specialty consult.	

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.

5.4.7. Treatment After Initial Evidence of Radiological Disease Progression

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

If radiologic imaging shows disease progression, after discussion between the sponsor and investigator, patients may continue to receive investigational products at the investigator's discretion 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, the patient must be re-consented via informed consent addendum and informed that in order to continue receiving the investigational products on study, the patient may be foregoing approved therapy with possible clinical benefit(s).

If the patient is subsequently found to have further disease progression at a subsequent tumor assessment, either radiologically according to Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) or clinically, then treatment with investigational products should be permanently discontinued.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational 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.

Any storage conditions stated in the SRSD, which is the IB, will be superseded by the storage conditions stated on the product labels.

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

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

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

5.5.1. Avelumab Storage

Avelumab must be stored in the refrigerator at 2°–8°C (36°–46°F). Do not freeze. Protect from light. Do not shake vigorously. See the Investigational Product Manual for storage conditions of avelumab once diluted.

5.5.2. Talazoparib Storage

Talazoparib is stored at room temperature (15°C–30°C; 59°F–86°F) or per approved local label.

Site staff will instruct patients on the proper storage requirements for take home investigational product, as talazoparib will be self-administered at home by patients.

5.6. Investigational Product Accountability

The investigative 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.

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.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment

Concomitant treatment considered necessary for the patient's well-being (ie, antiemetics, analgesics, megestrol acetate for anorexia) may be given at discretion of the treating physician.

All concomitant medications and treatments, including herbal supplements, supportive care drugs (eg, antiemetic treatment and prophylaxis), drugs used to treat adverse events or chronic diseases, blood products, and nondrug interventions (eg, paracentesis) will be recorded from 28 days prior to the start of study treatment (ie, the screening period) and up to 90 days after the last dose of investigational product (ie, the Short Term Follow-Up Day 90 Visit). If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new treatment is started.

5.7.1. Supportive Care

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

5.7.2. Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.[78]

In subsequent cycles, the use of hematopoietic growth factors is at the discretion of the treating physician in line with local guidelines. Erythropoietin or darbepoetin may be used at the investigator's discretion for the supportive treatment of anemia.

Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician.

5.7.3. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis of diarrhea, nausea and vomiting is permitted at the investigator's discretion. The choice of the prophylactic drug, as well as the duration of treatment, is up to the investigator and assuming the drug is not included in the Prohibited Concomitant Medications and Therapies section.

- **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.

5.7.4. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered, as needed, assuming the drug is not included in the Prohibited Concomitant Medications and Treatments section (Section 5.7.10).

5.7.5. Corticosteroids

Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes.[79] 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-CTLA4 compounds indicate that short-term use of steroids can be employed without compromising clinical outcomes.[81] Therefore, the use of steroids during this trial is restricted as follows while on avelumab treatment:

- Treatment of infusion-related reactions and irAEs, according to the modalities indicated in Section 5.4.6.4 and Section 5.4.6.5.
- Steroid replacement for adrenal insufficiency at physiologic doses equivalent to ≤10 mg prednisone daily is acceptable.
- Prophylactic use prior to CT or magnetic resonance imaging (MRI).
- Intranasal, inhaled topical steroids, eye drops, or local steroid injection (eg, intra-articular injection) are allowed.

See Section 5.7.10 Prohibited Concomitant Medications for information detailing specific prohibited uses of corticosteroids.

5.7.6. 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.

5.7.7. Androgen Deprivation Therapy for Patients with CRPC

Patients with CRPC must receive androgen deprivation therapy with a GnRH agonist/antagonist or bilateral orchiectomy (medical or surgical castration).

5.7.8. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and administration of investigational products required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping investigational products temporarily is recommended in case of a surgical procedure. Postoperatively, the decision to reinitiate treatment with investigational products should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

5.7.9. Concomitant Radiotherapy

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions and other sites of disease if considered medically necessary by the treating physician, provided that the bony lesions and/or other sites of disease to be irradiated were present at the time of the screening tumor assessments and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. All attempts should be made to rule out disease progression in the event of increased localized pain.

Study treatment should be withheld for the entire duration of palliative radiotherapy and can be restarted upon recovery from any radiotherapy-related toxicities, but no sooner than 48 hours after radiotherapy completion.

5.7.10. Prohibited Concomitant Medications 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.
- Radiation therapy (with the exception noted above in Section 5.7.8).
- Any investigational agents other than avelumab and talazoparib.
- Any vaccination for the prevention of infectious disease while on avelumab treatment, except for administration of inactivated vaccines.
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Prophylactic use of corticosteroids to prevent acute infusion-related reactions.

- Immunosuppressive drugs (ie, systemic corticosteroids) while on avelumab treatment, unless otherwise indicated for the treatment of irAEs or listed as an exception in Section 5.7.5. The following list of strong P-gp inhibitors that result in ≥2-fold increase in the AUC ratio of an in vivo probe P-gp substrate are prohibited: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, glecaprevir, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, pibrentasvir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, sofosbuvir, telaprevir, tipranavir, valspodar, velpatasvir, verapamil, and voxilaprevir. This list will be updated annually and reflected in the Talazoparib Investigator Brochure.

- Caution and monitoring for potential increased adverse reactions should be used upon concomitant use of the following transporter inhibitors with talazoparib: atorvastatin, azithromycin, conivaptan, curcumin, cyclosporine, diltiazem, diosmin, eliglustat, elacridar [GF120918], eltrombopag, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinensis extract. This list will be updated annually and reflected in the talazoparib Investigator Brochure.

If there is a clinical indication for one of the medications or vaccinations specifically prohibited during the trial, discontinuation from study treatment may be required. The investigator should consult with the sponsor about individual cases.

There are no prohibited therapies during the Short-Term and Long-Term Follow-up Phases.

6. STUDY PROCEDURES

6.1. Screening

For screening procedures see the Schedule of Activities and Section 7.

All screening activities must take place within 28 days prior to enrollment into the study, unless otherwise noted.

6.2. Treatment Period

For the treatment period procedures, see the Schedule of Activities and Section 7. For the treatment period, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following prioritization of events should be adhered to:

- Pharmacokinetic blood specimens – obtain at the scheduled time.

- Blood pressure/pulse rate –obtain prior to blood specimen collection and prior to dose.

- Clinical safety laboratory tests – must be performed pre-dose.

- Other procedures – All other procedures should be performed as close as possible to the scheduled time, but may be obtained before or after blood specimen collection, unless sampling is determined by the study personnel to potentially impact the results.

6.3. Patient Withdrawal/End of Treatment

For the End of Treatment Visit procedures, see Schedule of Activities and Section 7.

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

Reasons for withdrawal of study treatment may include:

- Objective disease progression. However, patients with disease progression who are continuing to derive clinical benefit from the study treatment will be eligible to continue study treatment, provided that the treating physician has determined that the benefit/risk for doing so is favorable (see Section 5.4.7 for details and exceptions);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two investigational products, the investigator may continue treatment with the other investigational product;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment;
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow-up may include:

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

6.3.1. Withdrawal of Consent

If the patient refuses further visits, the patient should continue to be followed for survival unless the patient withdraws consent for disclosure of future information or for further contact. 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. 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 or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient 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.

6.3.2. Lost to Follow-up

If a patient does not return for a scheduled visit, every effort should be made to contact the patient and report their ongoing status. This includes follow-up with persons authorized by 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.

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. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. 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.

6.4. Short-Term Follow-up Visits

For Short Term Follow-Up procedures, see Schedule of Activities (Table 1) and Section 7. All patients will be followed for safety every 30 days through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first.

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

If the patient has withdrawn from study treatment for a reason other than disease progression, the patient should continue to undergo tumor assessments during the Short Term Follow-Up period as if they were still on therapy, regardless if they start on a new anti-cancer therapy. See the Schedule of Activities (Table 1) for the frequency of tumor assessments during Short-Term Follow-Up.

6.5. Long-Term Follow-up Visits

After patients complete the Short Term Follow-Up period (90 days after the last dose of investigational product), patients will be followed for survival, independently of time of disease progression, and subsequent anti-cancer therapies every 12 weeks (±14 days) until death, lost to follow-up, patient withdrawal of consent, or study discontinued by the sponsor, whichever comes first. Contraception checks will be performed as applicable and for the duration described in Section 4.3. For Long Term Follow-Up procedures, see the Schedule of Activities (Table 1). These visits may be conducted in-clinic or by remote contact (eg, telephone).

If the patient has withdrawn from study treatment for a reason other than disease progression, the patient should continue to undergo tumor assessments during the Long Term Follow-Up period as if they were still on therapy, regardless if they start on a new anti-cancer therapy. In these cases, survival status will be collected at the time of the scheduled tumor assessments, which may be more or less frequent than the Long-Term Follow-Up visits (See Schedule of Activities, Table 1) for timing of tumor assessments in Long-Term Follow-Up Visits).

7. ASSESSMENTS

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

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

7.1. Safety Assessments

Safety assessments will include, but are not limited to, collection of AEs, serious adverse events (SAEs), vital signs, physical examination, 12-lead electrocardiogram (ECG), and laboratory assessments, including pregnancy tests, and verification of concomitant treatments. See the following sections regarding the specific safety assessments.

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL human chorionic gonadotropin (hCG) and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving study treatment (1 negative pregnancy test at screening and one at the baseline (Cycle 1 Day 1) visit immediately before study treatment administration).

Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy result will then be required at the baseline (Cycle 1 Day 1) visit before the subject may receive the study treatment. Pregnancy tests (serum or urine) will also be repeated on Day 1 of every cycle prior to dosing of either study drug during the active treatment period and at the End of Treatment visit to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed and when potential pregnancy is otherwise suspected, and may be repeated 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 products but may remain in the study only for Short-Term Follow-up and Long-Term Follow-up (see Sections 8.4.3 and 8.4.4 for required pregnancy follow-up and safety reporting requirements and the Schedule of Activities (Table 1) for Short-Term and Long-Term Follow-Up procedures).

7.1.2. Contraception Check

Male patients who are able to father children and female patients who are of childbearing potential, who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s), will need to affirm that they meet the criteria for correct use of contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his or her designee will instruct the patient to call immediately if one or both selected contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner (Section 4.3).

7.1.3. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by NCI CTCAE v 4.03), timing, seriousness, and relatedness.

7.1.4. Laboratory Safety Assessments

Blood samples and urine samples for safety laboratory assessments will be collected at the time points described in the Schedule of Activities and analyzed at local laboratories. The required safety laboratory tests are listed in Table 8. Required safety laboratory tests including at a minimum: hematology (hemoglobin, platelets, and white blood cells), and chemistry (ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose) must be reviewed prior to study drug administration on Days 1 and 15 of each treatment cycle.

Table 8. Required Safety Laboratory Tests

Hematology	**Chemistry**	**Coagulation**[a]	**Urinalysis**[a] **(Dispstick is acceptable)**	**Pregnancy Test**
Hemoglobin	ALT	INR	Urine dipstick for urine protein: If positive collect a microscopic (Reflex Testing)	For female patients of childbearing potential, serum or urine with a sensitivity of at least 25 mIU/mL
Platelets	AST	PTT or aPTT		
WBC	Alkaline Phosphatase			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium		Urine dipstick for urine blood: If positive collect a microscopic (Reflex Testing)	
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Total Bilirubin[b]			
Thyroid Function Tests:	BUN or Urea			
TSH, Free T4	Creatinine			
	Uric Acid			
	Glucose (non-fasted)			
Other Tests:	Albumin			
ACTH	Phosphorus or Phosphate			
HBV surface antigen	Total Protein			
Anti-HCV antibody	Amylase			
If Anti-HCV antibody test positive, then HCV RNA	Gamma Glutamyl Transferase (GGT)			
Testosterone *(at screening only for CRPC patients)*	Creatine Kinase			
	C-reactive Protein (CRP)			
	Lactate Dehydrogenase (LDH)			
	Lipase			

Abbreviations used in the table: ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, CRPC=castration-resistant prostate cancer, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, PTT=partial thromboplastin time, aPTT=activated partial thromboplastin time, RNA=ribonucleic acid, TSH=thyroid-stimulating hormone, WBC=white blood cell.

[a] Required at screening then to be performed as clinically indicated.

[b] For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, INR international normalized ratio, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

7.1.5. Physical Examinations and Vital Signs

Patients will have full physical examination at screening. Subsequent visits will include major body systems (focused and/or as clinically indicated), vital signs, assessment of ECOG performance status (see Appendix 2), weight and height (height will be measured at screening only) at the time points described in Schedule of Activities (Table 1).

Vital signs, to include blood pressure, pulse rate and temperature will be also recorded at the time points described in the Schedule of Activities (Table 1). Vitals signs should be taken prior to administration of any investigational products at the visit.

7.1.6. (12-Lead) Electrocardiograms

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 baseline. Thereafter, on treatment ECGs will be performed as clinically indicated.

Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc >500 msec, a subsequent 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. Pharmacokinetics Assessments

All efforts will be made to obtain the PK samples at the scheduled nominal time relative to dosing. However, the exact time of the sample collection will always be noted on the CRF. For samples where nominal time coincides with end of infusion, a sample collected within 10 minutes post end of infusion will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF). If 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 sampling schedule may be modified based on emerging PK data.

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.

As part of understanding the PK of the investigational products, samples may be used for metabolite identification and/or further bionalaytical evaluation, as well as for other internal exploratory purposes. These data will not be included in the Clinical Study Report (CSR). Samples collected for this purpose will be retained in accordance with local regulations and, if not used within this timeframe, will be destroyed.

7.2.1. Blood for PK Analysis of Avelumab

Blood samples (3.5 mL whole blood at each time point) will be collected for PK analysis of avelumab, as outlined in the Schedule of Activities (Table 2). Pre-dose avelumab PK samples will be collected within 1 hour prior to taking talazoparib dose. 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

Blood samples (3 mL whole blood at each time point) will be collected for PK analysis of talazoparib as outlined in the Schedule of Activities (Table 2). Pre-dose talazoparib PK samples will be collected within 1 hour prior to taking talazoparib dose. The post-dose talazoparib PK samples should be taken within 10 minutes after the avelumab infusion ends, corresponding to approximately 2 hours after talazoparib dosing. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

7.3. Immunogenicity Assessments

Blood samples (3.5 mL whole blood) will be collected for assessment of avelumab Anti-Drug Antibodies (ADAs), as outlined in the Schedule of Activities (Table 2). Predose ADA samples will be collected within 2 hours prior to talazoparib dosing. Please refer to the Laboratory Manual for instructions for specific details on collection tubes, processing and shipping.

For all patients, blood for ADA samples will be drawn from the contralateral arm of the avelumab infusion.

Immunogenicity blood samples will be assayed for ADA using a validated assay in compliance with Pfizer standard operating procedures. The sample analysis will follow a tiered approach of screening, confirmation, and titer determination. Samples tested positive for ADA may be further analyzed for Nab using a validated assay in compliance with Pfizer standard operating procedures. Additional details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Laboratory Manual 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.

As part of understanding the immunogenicity of avelumab, samples may be used for evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the CSR.

7.4. Biomarker and Pharmacodynamic Assessments

The key objectives of the biomarker analyses that will be performed in this study are to:

- Centrally confirm BRCA1, BRCA2 and ATM gene defects;
- Assess the utility of ctDNA as an alternative to tissue based testing for selection of patients with BRCA1, BRCA2 and ATM defects;
- Investigate candidate biomarkers in baseline tissue, ctDNA and blood that may have predictive value in identifying those patients, within the eligible population for this study, who are most likely to benefit from treatment with the combination of avelumab and talazoparib;
- Investigate candidate biomarkers in on treatment and post treatment tissue and blood samples that will help to confirm the mechanism of action and/or resistance for the combination.

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;
- The number and phenotype of infiltrating immune cells;
- Expression of a panel of genes or presence of a specific gene signature;
- Frequency and diversity of different TCR sequences;
- Tumor mutational burden and loss of heterozygosity;
- Presence of mutations in key oncogenes;
- Levels of a panel of proteins or presence of a specific proteomic signature;
- Presence of a specific epigenetic signature.

Information about PD-L1 expression will be collected at Screening, as part of patient's cancer history, for all patients with prior available results.

7.4.1. Tumor Tissue Samples

7.4.1.1. Pretreatment Tumor Tissue Samples

All patients must provide formalin-fixed paraffin-embedded (FFPE) tumor tissue as outlined in one of the options below. Availability of tumor tissue sample must be confirmed during screening prior to enrollment, and sample must be sent within 28 days after enrollment.

Note that in all cases where slides are provided, positively-charged glass slides should be used and the slides generated should contain tumor tissue sections that are 4-5 microns thick and the slides should not be stained or baked. All tumor tissue sections provided should ideally measure 5×5 mm and must contain 40% or greater tumor nuclei.

Where local or regional regulations prevent submission of FFPE tissue blocks, the requisite number of slides indicated below generated from the indicated block may be provided.

Option 1 For patients whose local BRCA/ATM test was conducted on a tissue sample collected ≤24 months prior to enrollment, where the sample is still available and sufficient to provide at least 20 slides	The following tissue should be provided from the same sample used to derive the historic test result that supported study eligibility: • An original (not recut) H&E slide together with a block containing sufficient tumor tissue to generate at least 20, but preferably 25 slides. • Where an older archive block (ie, collected >24 months prior to enrollment) is also available, this block should also be submitted if it contains sufficient tumor tissue to generate at least 10 slides.
Option 2 For patients whose local BRCA/ATM test was conducted on a tissue sample collected ≤24 months prior to enrollment, where the sample is still available and sufficient to provide at least 15, but less than 20 slides. OR For patients whose local BRCA/ATM test was conducted on a tissue sample collected >24 months prior to enrollment, where the sample is still available and sufficient to provide at least 15 slides.	The following tissue should be provided from the same sample used to derive the historic test result that supported study eligibility: • An original (not recut) H&E slide together with a block containing sufficient tumor tissue to generate at least 15 slides. • An additional block should also be submitted, from a second sample collected ≤24 months prior to enrollment, containing sufficient tumor tissue to generate at least 5, but preferably 10 slides. • Where an older archive block (ie, collected >24 months prior to enrollment) is also available, this block should also be submitted if it contains sufficient tumor tissue to generate at least 10 slides.

Option 3 For patients whose local BRCA/ATM test was conducted on a tissue sample that is no longer available, or is insufficient to provide at least 15 slides. OR For patients whose local BRCA/ATM test was conducted on germline DNA.	The following tissue should be provided from a tissue sample collected ≤24 months prior to enrollment: • An original (not recut) H&E slide together with a block containing sufficient tumor tissue to generate at least 20, but preferably 25 slides. • Where an older archive block (ie, collected >24 months prior to enrollment) is also available, this block should also be submitted if it contains sufficient tumor tissue to generate at least 10 slides.

In all instances above, when no tissue sample collected within 24 months prior to study enrollment is available, a core biopsy from a locally recurrent or metastatic tumor site (that is not the only RECIST v1.1 target lesion) must be performed during screening to provide a FFPE tumor tissue block or the required number of slides specified above. The biopsy is to be performed using a minimum 18 gauge needle, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested for each biopsy procedure. Tissue derived from cytologic sampling cannot be submitted.

For non-prostate cancer patients, if a tissue sample collected within 24 months from study enrollment is not available, and no lesion that can be biopsied outside of bone is present, tumor tissue collected within 5 years prior to study enrollment may be provided.

For prostate cancer patients, if a tissue sample collected within 24 months from study enrollment is not available, and no lesion that can be biopsied outside of bone is present, then fresh bone biopsies are acceptable. In other instances, tissue from bone biopsies should not be submitted.

See the Laboratory Manual for additional details on the handling of tissue samples including processing, storage, and shipment.

7.4.1.2. On Treatment and End of Treatment Tissue Samples

In addition to the pre-treatment tumor tissue described above, tumor tissue is requested (optional) for those patients who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period. In addition, every effort should be made to perform a tumor biopsy at the time of RECIST v1.1 confirmed disease progression (for all patients except mCRPC) or PCWG3 confirmed disease progression (for mCRPC patients only) if a patient discontinues study treatment due to disease progression, except in instances where the procedure, as performed in the clinical research setting, poses an unacceptable risk to the patient. A 14-day window is permitted.

These samples will be used to assess one or more of the biomarkers listed above in Section 7.4, with the aim of determining mechanisms of response and resistance to treatment.

See the Laboratory Manual for additional details on the handling of all tissue samples including processing, storage, and shipment.

7.4.2. Peripheral Blood Samples

As described in the Schedule of Activities, the following blood samples and subsequent analyses will be conducted:

- Blood samples (6 mL whole blood) will be collected to assess the frequency and diversity of TCR sequences before, during and at the end of treatment;
- Blood sample (20 mL whole blood for processing to plasma) will be collected before, during and at the end of treatment, for isolation of circulating tumor DNA (ctDNA). This sample will be used to analyze genetic biomarkers, including defects in BRCA 1/2 and ATM and TMB that may relate to response to resistance to treatment;
- Blood samples (4 mL whole blood for processing to plasma) will be collected before and at the end of treatment to assess proteomic and metabolomic factors and signatures that may relate to response or resistance;
- Blood samples (2 x 2.5 mL whole blood) will be collected and processed to generate RNA before and at the end of treatment. 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 before treatment and processed to generate genomic DNA. DNA will be used to assess potential epigenetic or genetic biomarkers that may relate to response to treatment, including the presence of germline defects in BRCA1, BRCA2 and ATM.

7.4.3. Additional Analyses

Analyses in addition to those described above may be warranted based on emerging data and technologies. 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. To enable these analyses, specimens including whole blood, serum, plasma, RNA, DNA and residual tissue will be stored for subsequent analyses, unless prohibited by local regulation or by decision of the IRB or EC.

7.5. Banked Biospecimens

Banked biospecimens will be collected from patients for exploratory research relating to the avelumab and talazoparib combination treatment response in patients with locally advanced or metastatic solid tumors. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each

patient's privacy and confidentiality. Banked biospecimens will be assigned the patient's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the patient's ID and the patient's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also post-marketing research. Patients may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis) will be collected at the time specified in the Schedule of Activities section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to avelumab and talazoparib combination treatment in patients with locally advanced or metastatic solid tumors. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

The banked biospecimens will be collected from all patients unless prohibited by local regulations or IRB/EC decision.

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

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 biospecimen 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 Assessment

Tumor response assessments are dependent upon the patient's tumor type. All tumor types, except mCRPC, will perform tumor assessments, as per the requirements described in this section. For tumor response assessments that are unique for patients with mCRPC, see Section 7.6.1.

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis CT or MRI scans. Baseline Brain CT or MRI scan is required for all patients at baseline (Screening); patients with stable brain metastases present at baseline (Screening) will continue to have brain CT or MRI scans performed at each tumor assessment. Otherwise, brain CT or MRI imaging is required only when clinically indicated if new brain metastases are suspected.

Bone scans (preferred method) or 18-fluorodeoxyglucose positron emission tomography (^{18}F- FDG-PET)/CT or MRI is required for all patients at baseline (Screening). If bone metastases are present at baseline (screening), then repeat bone imaging is required every 16 weeks for the first 52 weeks of study treatment and every 24 weeks thereafter. Otherwise, bone imaging is required only if new bone metastases are suspected. Bone imaging is also required at the time of confirmation of CR for patients who have bone metastases.

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 (Screening) will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline (Screening), during treatment every 8 weeks for 52 weeks from the start of the study treatment, and then every 16 weeks thereafter until documented confirmed disease progression by BICR assessment regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities (Table 1). In addition, radiological tumor assessments will also be conducted whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks and the prior response is other than confirmed PD).

Timing of disease assessment should follow calendar days and should not be adjusted for delays in cycle starts.

In case CR or PR is observed, tumor assessments must be confirmed on repeated imaging at least 4 weeks after initial documentation. The allowable time window for tumor assessments is ±7 days.

Assessment of response will be made using RECIST v1.1 (see 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.

Details of treatment after initial evidence of radiological disease progression are provided in Section 5.4.7.

Expedited Blinded Independent Central Review for Disease Progression

Since the primary endpoint of the study is OR based on BICR assessment (CR or PR per RECIST v1.1 from the first dose of study treatment until disease progression), expedited BICR review will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from screening 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 the radiographic image review, unless contraindicated by the investigator.

All patients' files and radiologic images must be available for source verification and for potential peer review.

Management of incidental findings

An incidental finding is one unknown to the patient that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study. Radiographic images will be reviewed by a central review facility.

The purpose of this review is to evaluate images for BICR. Central image review is not a complete medical review of the subject and no incidental findings will be shared with the principal investigator, site staff, or the patient. All safety reviews will be the sole responsibility of site staff.

7.6.1. mCRPC Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging is categorized as soft tissue (including nodes, viscera and prostate/prostate bed [primary site]) or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis. Bone imaging must be whole body radionuclide bone scan (scintigraphy). Bone scans and brain CT or MRI scans are required for all patients at baseline (Screening). Patients with stable brain metastases present at baseline (Screening) will continue to have brain CT or MRI scans performed at each tumor assessment. Otherwise, brain CT or MRI imaging is required only when clinically indicated if new brain metastases are suspected.

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 (Screening) will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at baseline (Screening), during treatment every 8 weeks for 24 weeks from the start of the study treatment, and then every 12 weeks thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities (Table 1), whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks and the prior response is other than confirmed PD). Timing of disease assessment should follow calendar days and should not be adjusted for delays in cycle starts.

Assessment of response will be made using RECIST v1.1 (see Appendix 3). The investigator will assess response of soft tissue disease by RECIST v1.1. Bone disease will not be considered as non-target lesions assessed by RECIST v1.1, but will be assessed for progressive disease by PCWG3.[64] The documentation required for the determination of radiographic progression is shown in Appendix 4.

An objective response is defined as a best overall response of CR or PR per RECIST v1.1 and must be confirmed on repeated imaging at least 4 weeks after initial documentation. Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3. The allowable time window for tumor assessments is ±7 days. See Appendix 4 for the timing of confirmatory imaging requirements.

Other requirements for tumor assessment management that are not unique to mCRPC, including BICR expedited review and treatment after initial evidence of radiological disease progression, are to be followed as per Section 7.6.

7.7. Blood Tests for Tumor Markers and Circulating Tumor Cells

7.7.1. CA-125 for Patients with Ovarian Cancer

For patients with ovarian cancer, blood will be collected at the time points described in the Schedule of Activities (Table 1) and analyzed at local laboratories for cancer antigen 125 (CA-125) testing.

7.7.2. Prostate-Specific Antigen for Patients with mCRPC

For patients with mCRPC, blood will be collected at the time points described in the Schedule of Activities (Table 1) and analyzed at local laboratories for prostate-specific antigen (PSA).

7.7.3. Circulating Tumor Cells (CTCs) for Patients with mCRPC

For patients with mCRPC, blood will be collected at the time points described in the Schedule of Activities (Table 1) and analyzed at the central laboratory to allow quantitation of CTCs.

7.8. Patient Reported Outcome Assessments

The instruments proposed are the EORTC QLQ-C30 (all patients), EORTC QLQ-OV28 (ovarian cancer patients), EORTC QLQ-BR23 (breast cancer patients), EORTC QLQ-PR25 (prostate cancer patients) and the EQ-5D-5L (all patients) to capture disease and treatment-related symptoms and health-related quality of life (HRQoL) as exploratory endpoints. Selected items/symptoms will also be included from the Patient Reported Outcome - Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library to capture patient reported symptomatic AEs, as an exploratory endpoint (all patients). The PRO instruments selection and administration schedule have been considered with patient burden in mind. The ePRO device training is to be provided to the patients at enrollment and the site coordinator should ensure patient understanding and ability to use the device. All PRO assessments will be administered per the Schedule of Activities (Table 1). The assessments are not required to be completed if a patient does not understand the language(s) available for a specific questionnaire and cannot complete the specific questionnaire independently.

7.8.1. EuroQoL EQ-5D-5L

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 (Appendix 5).[66,67] 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.[67] 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.

7.8.2. EORTC QLQ-C30

The EORTC QLQ-C30 is a published, validated and self-administered patient reported outcome questionnaire (Appendix 6).[68,69] The EORTC QLQ-C30 is a 30-question survey and includes 5 functional domain subscales, including a physical functioning sub-scale, a role functioning subscale, an emotional functioning sub-scale, a cognitive functioning sub-scale and a social functioning subscale. Higher scores on the functioning domains are indicative of higher levels of functioning. Oncology-related symptoms of the EORTC QLQ-C30 include fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact (1 item each). Higher scores are reflective of a greater presence of symptoms. The amount of time for a patient to complete the EORTC QLQ-C30 questionnaire is estimated to be about 10 minutes.

7.8.3. EORTC QLQ-OV28

The EORTC QLQ-OV28 is the ovarian cancer-specific module of the EORTC quality of life questionnaire (Appendix 7).[68,70,71] The EORTC QLQ-OV28 is a 28 item instrument with seven (7) functional domain subscales. The 7 subscales include: (i) an abdominal/gastrointestinal symptom subscale (7 items); (ii) a peripheral neuropathy subscale (3 items); (iii) an other chemotherapy side effects subscale (7 items); (iv) a hormonal/menopausal symptoms subscale (2 items); (v) a body image subscale (2 items); (vi) an attitude to disease and treatment subscale (3 items) and (vii) a sexual function subscale (4 items). Similar to the EORTC QLQ-C30 higher scores are reflective of a greater presence of symptoms.

The amount of time for a patient to complete the EORTC QLQ-OV28 questionnaire is estimated to be about 10 minutes.

7.8.4. EORTC QLQ-BR23

The EORTC QLQ-BR23 is the breast cancer-specific module of the EORTC quality of life questionnaire (Appendix 8).[68,72] The EORTC QLQ-BR23 is a 23 item instrument with five functional domain subscales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea & vomiting, and pain), and several single items, as well as a module designed specifically for breast cancer. Similar to the EORTC QLQ-C30 higher scores are reflective of a greater presence of symptoms.

The amount of time for a patient to complete the EORTC QLQ-BR23 questionnaire is estimated to be about 10 minutes.

7.8.5. EORTC QLQ-PR25

The EORTC QLQ-PR25 is the prostate cancer-specific module of the EORTC quality of life questionnaire(Appendix 9).[73] The EORTC QLQ-PR25 is a 25 item instrument with four subscales for the assessment of urinary symptoms (9 items), bowel symptoms (4 items), hormone treatment-related symptoms (6 items) and sexual activity and function (6 items). Similar to the EORTC QLQ-C30 higher scores are reflective of a greater presence of symptoms.

The amount of time for a patient to complete the EORTC QLQ-PR25 questionnaire is estimated to be about 10 minutes.

7.8.6. PRO-CTCAE

Initiated and sponsored by the US National Cancer Institute, the PRO-CTCAE is a patient-reported outcome measure developed to evaluate symptomatic toxicity in patients enrolled in cancer clinical trials (Appendix 10).[74] It was designed to complement the Common Terminology Criteria for Adverse Events (CTCAE), the standard lexicon for investigator or clinician-reported adverse events in cancer trials.

The PRO-CTCAE item library is composed of 124 self-report items reflecting 78 symptomatic adverse events drawn from the CTCAE arranged by organs and systems. Each adverse event is assessed relative to one or more attributes that include the presence/absence/amount (P), frequency (F), severity (S), and interference (I) with usual or daily activities. PRO-CTCAE provides a systematic yet flexible tool for descriptive reporting of symptomatic treatment side effects in cancer clinical trials.

The items selected from the PRO-CTCAE item library for use in this study was based on AEs for the medicinal products included in this clinical trial: the AE profiles for avelumab (Avelumab Investigators Brochure V7), and talazoparib (Talazoparib Investigators Brochure 2017), General class effects, mechanism of action, and route of administration were also considered, but no additional PRO-CTCAE items were identified for inclusion. Item selection occurred in an unbiased fashion and items were considered for inclusion if it appeared in any of the AE profiles. Information collected in other PROs was considered to minimize patient burden when feasible, but duplications were not always eliminated given the other PROs have a different administration schedule. There are no known drug-drug interactions to suggest enhanced or new AEs as a result of avelumab + talazoparib combination. The items selected were: rash, hair loss, itching, headache, muscle pain, joint pain, decreased appetite, nausea, vomiting, constipation, diarrhea, abdominal pain, insomnia, fatigue, shortness of breath, cough, dizziness, and chills. Some of the items include follow-up questions.

PRO-CTCAE is an exploratory instrument for collecting patient reported symptoms and item responses will be analyzed for descriptive reporting purposes at the end of the study. PRO-CTCAE data will be collected, analyzed and reported separately from CTCAE AE data and will not be reconciled with each other. Adverse events for this study will be assessed, recorded, and reported in the standard manner with investigators using CTCAE.

The informed consent will inform the patients that their responses on the PRO-CTCAE will not be routinely reviewed during the study by their physician until the end of the study, unless local regulations or ethics committee decision mandate differently. Patients will be instructed to share any and all information with their physicians, including responses on the PRO-CTCAE. A reminder of the same instruction/disclaimer will also be given at the start of the PRO-CTCAE questionnaire and a check box at the end for patient acknowledgement on this disclaimer. While PRO-CTCAE responses are not routinely reviewed by the physician, if a physician is made aware of information that may constitute an adverse event, it should be reported in accordance with Adverse Event Reporting Section 8 of the protocol. Similarly, in the event a patient conveys information/response information that they entered into the PRO-CTCAE, to their study physicians, the study physician should consider this information in the context of whether Adverse Event Reporting Section 8 of the protocol is applicable.

PRO-CTCAE responses are scored from 0 to 4, and there are as yet no standardized scoring rules for how to combine attributes into a single score or how best to analyze PRO-CTCAE data longitudinally. PRO-CTCAE scores for each attribute (frequency, severity and/or interference) should be presented descriptively (eg, summary statistics or graphical presentations). CTCAE grades for the corresponding time period should be presented in conjunction with PRO-CTCAE scores.[76]

PRO-CTCAE in this trial will only be administered in countries where certified translations are already available from the NCI. These assessments are not required to be completed if a patient does not understand the language(s) available for a specific questionnaire and cannot complete the specific questionnaire independently. The amount of time for a patient to complete the questionnaire is estimated to be about 5 minutes.

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 suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

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

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

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient Withdrawal/End of Treatment section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

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

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the

investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);

- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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

8.2.2. Abnormal Test Findings

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

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

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

8.2.3. Serious Adverse Events

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

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

Or that is considered to be:

- An important medical event.

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

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

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

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);

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

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

8.3. Severity Assessment

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

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

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

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

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 liver function test (LFT) abnormalities has yet been found. Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

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

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

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

8.4.4. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.4.4.1. 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.

8.4.4.2. Occupational Exposure

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

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

8.4.5. Medication Errors

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

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

8.4.5.1. Medication Errors

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

Medication errors include:

- Medication errors involving patient exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

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

In the event of 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

This section describes the data analysis and statistical methods for each of the cohorts evaluated in this study and are further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Analysis Sets

9.1.1. Full Analysis Set

The full analysis set includes all enrolled patients who receive at least 1 dose of study treatment. Patients will be classified according to the cohort assigned at enrollment.

9.1.2. Safety Analysis Set

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

9.1.3. Pharmacokinetics Analysis Sets

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 lower limit of quantitation (LLQ) for 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 for avelumab or talazoparib.

9.1.4. Immunogenicity Analysis Set

The immunogenicity analysis set is a subset of the safety analysis set and will include patients who have at least 1 ADA/Nab sample collected for avelumab.

9.1.5. Biomarker Analysis Sets

The biomarker analysis set includes all patients in the safety analysis set who have at least 1 screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

9.1.6. PRO-CTCAE Analysis Set

The PRO-CTCAE analysis set is a subset of the safety analysis set and will include patients with baseline (Day 1 of Cycle 1) and at least one post-baseline assessment of the selected items from the PRO-CTCAE item library.

9.2. Sample Size Determination

The primary endpoint is confirmed OR in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by BICR using RECIST v1.1 and, in patients with mCRPC, RECIST v1.1 and PCWG3.

Up to approximately 150 patients will be enrolled in Cohort 1 and 50 patients in Cohort 2. Thus, a total of approximately 200 patients will be enrolled.

With 150 and 50 treated patients in Cohort 1 and Cohort 2, respectively, ORR can be estimated with a maximum standard error of 0.041 and 0.071, respectively. Assuming a beta (0.5, 0.5) prior:

- Cohort 1: if 66 responders (out of 150 patients, ORR of 44%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.841);

- Cohort 2: if 23 responders (out of 50 patients, ORR of 46%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.807).

Table 9 provides the exact 95% confidence intervals for ORR based on different observed number of responders in a given tumor type cohort.

Table 9. Sample Size and Exact 95% Confidence Intervals for ORR

N per Cohort	Number of Responders	Observed ORR	Exact 95% CI for ORR
50	20	40%	26.4% - 54.8%
	23	46%	31.8% - 60.7%
	25	50%	35.5% - 64.5%
	27	54%	39.3% - 68.2%
	28	56%	41.3% - 70.0%
	30	60%	45.2% - 73.6%
	32	64%	49.2% - 77.1%
	35	70%	55.4% - 82.1%
150	60	40%	32.1% - 48.3%
	66	44%	35.9% - 52.3%
	75	50%	41.7% - 58.3%
	83	55%	47.0% - 63.4%
	90	60%	51.7% - 67.9%
	98	65%	57.1% - 72.9%
	105	70%	62.0% - 77.2%

CI=confidence interval; ORR=objective response rate.

9.3. Efficacy Analysis

All efficacy analyses will be performed based on the full analysis set, separately by cohort and for both cohorts combined.

9.3.1. Analysis of the Primary Endpoint

The primary endpoint is confirmed OR by BICR assessment.

- For patients with solid tumors, except mCRPC:

Objective response (OR) is defined as a CR or PR per RECIST v1.1 from the first dose of study treatment until disease progression or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. ORR is defined as the proportion of patients with a confirmed CR or PR according to RECIST v1.1. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the patient will be counted as a non-responder in the assessment of ORR. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the assessment of ORR. The 2-sided exact 95% CIs for ORR will be calculated.

- For patients with mCRPC:

Objective response (OR) is defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST v1.1 from the first dose of study treatment until disease progression or death due to any cause. Soft tissue responses will be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression per PCWG3 criteria. The radiographic assessment of soft tissue disease will use RECIST v1.1 (see Appendix 3), and bone disease will be evaluated per PCWG3 (see Appendix 4).

9.3.2. Analysis of the Secondary Endpoints

Objective response (OR) based on investigator assessment will also be summarized as described in Section 9.3.1. The secondary endpoints TTR, DR, and PFS will be summarized separately based on BICR assessments and based on investigator assessment.

For patients with solid tumors, except mCRPC:

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

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

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

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

- TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, and OS will be analyzed using Kaplan-Meier methods and descriptive statistics. Point estimates will be presented with 95% CIs. In addition, progression date, death date, date of first response, and last tumor assessment date will be listed, along with Best Overall Response (BOR), TTR, DR, PFS and OS.

For patients with mCRPC:

- TTR is defined as the time from the first dose of study treatment to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a BOR of CR or PR per RECIST v1.1. The response must be confirmed at least 4 weeks later with a repeated CT/MRI;

- DR is defined for patients with confirmed objective response (CR or PR) as the time from the first objective evidence of soft tissue response (subsequently confirmed) per RECIST v1.1 and no evidence of confirmed bone disease progression by PCWG3 to the first subsequent objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression evaluated per RECIST v1.1 or bone disease progression evaluated per PCWG3 (see Appendix 4);

- PFS is defined as the time from the first dose of study treatment to documentation of radiographic progression in soft tissue evaluated per RECIST v1.1, in bone evaluated per PCWG3, or death, whichever occurs first (see Appendix 4). Details associated with censoring will be presented in the SAP;

- PSA response is defined as the proportion of patients with confirmed PSA decline ≥50% compared to baseline. PSA response will be calculated as a decline from baseline PSA (ng/mL) to the maximal PSA response with a threshold of 50%. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. The proportion of patients with confirmed PSA decline ≥50% compared with baseline will be calculated along with 95% Cis;

- Time to PSA progression is defined as the time from the first dose to the date that a ≥25% increase in PSA with an absolute increase of ≥2 μg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later. Details associated with censoring will be presented in the SAP;

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

- TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, time to PSA progression and OS will be analyzed using Kaplan Meier methods and descriptive statistics. Point estimates will be presented with 95% Cis;

- CTC count conversion is defined as a decrease in CTC count from ≥5 CTC per 7.5 mL of blood at baseline to <5 CTC per 7.5 mL of blood anytime on study. CTC0, defined as a decrease in CTC count from ≥1 CTC per 7.5 mL to an undetectable level anytime on study, will also be reported. The proportion of patients with CTC count conversion and CTC0 will be calculated along with 95% CIs.

For patients with ovarian cancer:

- CA-125 response is defined as at least a 50% reduction in CA-125 levels from baseline. The response must be confirmed and maintained for at least 28 days. The proportion of patients with CA-125 response will be calculated along with 2-sided exact 95% CIs.

9.4. Analysis of Pharmacokinetics and Pharmacodynamics

9.4.1. Analysis of Pharmacokinetics of Investigational Products

Pharmacokinetic data analyses will include pre-dose and post-dose sampling for serum avelumab and plasma talazoparib concentrations on Days 1 and 15 of Cycle 1 and on Day 1 of Cycle 3 for both talazoparib and avelumab, and additionally on Day 1 of Cycles 6, 12, 18, and 24 for avelumab only. PK data analyses will include descriptive summary statistics of the pre-dose/trough (C_{trough}) concentrations for both investigational products and post-dose (for talazoparib) or maximum (C_{max}) concentrations (for avelumab) for each cycle. Other PK parameters may be determined if deemed appropriate. Additional summary statistics will be presented for avelumab across all treatment groups by study phase as well as combined across both study phases. For talazoparib, summary statistics will also be presented combined for all patients. The summary data will be compared with the historical data of avelumab and talazoparib as single agents to assess the effect of avelumab on the PK of talazoparib and the effect of talazoparib on the PK of avelumab.

The pre-dose/trough and post-dose/C_{max} concentrations for avelumab and talazoparib will be plotted using box whisker plots by cycle and day within cycle for the subsets of data corresponding to the summary statistics described above.

9.4.2. Population Pharmacokinetic Analysis or Pharmacokinetic/Pharmacodynamic (PK/Pharmacodynamic) Modeling

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies investigating avelumab and/or talazoparib to: 1) further assess the effect of talazoparib on the PK of avelumab and/or avelumab on the PK of talazoparib, and 2) explore any association between study drug exposure and biomarkers or significant safety endpoints. If performed, the details of these analyses will be outlined in a separate pharmacometric analysis plan (PMAP). The results of these analyses, if performed, may be reported separately.

9.4.3. Analysis of Biomarker Secondary and Exploratory Endpoints

All analyses of biomarkers will be performed based on the biomarker analysis set, separately by cohort and pooled across cohorts.

Biomarker data will include baseline and on-treatment/end of treatment levels of and changes in biomarkers including, but not limited to, centrally assessed defects in BRCA1, BRCA2 and ATM in tumor tissue and ctDNA, PD-L1 expression, and TMB in tumor tissue, TMB in ctDNA, germline defects in BRCA1, BRCA2 and ATM. Tumor mutational burden (TMB), is defined as the total number of mutations in the tumor genome, or number of mutations per megabase of DNA if derived from targeted sequencing.

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

For discrete measurement biomarkers (eg, tumor marker status), frequencies and percentages of categorical biomarker measures will be determined at 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 rank-sum test, Kaplan-Meier estimates, and linear regression as appropriate. The statistical approaches will explore the correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

9.4.4. Analysis of Immunogenicity Data of Avelumab

ADA/Nab data for avelumab will be listed and summarized.

The percentage of patients with positive ADA and Nabs each will be summarized by cohort and, if deemed appropriate, combined across all cohorts. 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 and pharmacokinetics may be evaluated, if data permit.

9.5. Safety Analysis

All safety analyses will be performed based on the safety analysis set separately by cohort and pooled across cohorts.

9.5.1. Adverse Events

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

9.5.2. Laboratory Test Abnormalities

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

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

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

9.5.3. Electrocardiogram

Baseline ECG measurements will be summarized by cohort. 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, and QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval.

9.6. Analysis of Other Endpoints

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

9.6.1. PRO-CTCAE

The PRO-CTCAE analysis will be based on the PRO-CTCAE analysis set.

Descriptive statistics [mean, standard deviation, median, range and 95% CI] will be generated for the responses on each selected item from the PRO-CTCAE item library, by cohorts and overall, with and without using the 'baseline subtraction' method. In PRO data analyses generally, an approach frequently used to adjust for baseline scores is to tabulate change from baseline. However, for adverse event reporting a different approach is more synonymous with clinician CTCAE grading and may improve the attribution of symptoms to specific treatments. Specifically, for any given patient, the worst adverse event during treatment is tabulated only for adverse events that are worse than the baseline score. For example, if a patient had nausea at baseline with a magnitude score of 2, and his or her worst post-baseline score was 1 or 2, then no AE would be tabulated for that patient (ie, a score of 0). However, if that patient's worst post-baseline score was 3 or higher, then that post-baseline score would be tabulated for that patient.[76] CTCAE grades for the corresponding time period will also be presented in conjunction with PRO-CTCAE scores.

9.7. Analysis of Patient Reported Outcomes

The full analysis set will be used for the EORTC QLQ-C30, OV-28, BR23, QLQ-PR25, and EQ-5D-5L analyses. The data from Cohort 1 will be used for QLQ-OV28, QLQ-PR25, and QLQ-BR23.

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 EORTC QLQ-C30 (all patients), EORTC QLQ-OV28 (ovarian cancer patients in Cohort 1), EORTC QLQ-BR23 (breast cancer patients in Cohort 1), QLQ-PR25 (prostate cancer patients in Cohort 1) and the EQ-5D-5L (all patients). The mean change of absolute scores from baseline (and 95% CI) over time will also be reported. Line charts depicting the means and mean changes with

standard error (SE) over time will be provided overall and for each cohort. 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.

9.8. Interim Analysis

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/Pharmacodynamic modeling, and/or to support clinical development.

An interim analysis will be performed to allow early termination of the cohorts for futility. Within each cohort, ORR based on confirmed PR or CR by BICR assessment will be estimated after at least 20 patients are treated and followed for 24 weeks, without holding patient enrollment in either cohort. If based on the observed ORR, the probability of a true ORR ≥40% is ≤0.05 then the cohort will be stopped for futility. For example if 4 or less responders are observed out of 20 patients treated in a cohort (ORR ≤20%) after the minimum follow-up specified above, then the cohort will be stopped for futility.

9.9. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

In most cases, the source documents are the hospital or the physician patient 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 patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Patient Information and Consent

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

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

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

The informed consent document 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 or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant 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.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Document (ICD).

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

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 a Member State

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

13.2. End of Trial in All Other Participating Countries

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

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 and/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 (CSR 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.

16. REFERENCES

1. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001; 2(3):261-8.

2. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016; 54:139-48.

3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17(5):405-24.

4. Investigator's Brochure Version 8, Avelumab (MSB0010718C). 16 May 2018.

5. BAVENCIO® (avelumab) injection, for intravenous use [prescribing information]. New York, NY: EMD Serono, Inc. and Pfizer Inc; 2017.

6. BAVENCIO® (avelumab) [summary of product characteristics]. London, UK: Merck Serono; 2017.

7. Pfizer press release. Available: https://www.pfizer.com/news/press-release/press-release-detail/bavencio_avelumab_approved_for_merkel_cell_carcinoma_in_japan. Accessed on 22 Jan 2018.

8. BAVENCIO® (avelumab) [Australian Register of Therapeutic Goods (ARTG), Public Sumary]. Frenchs Forest, Australia: Merck Serono; 2018.

9. Shen Y, Aoyagi-Scharber M, Wang B. Trapping poly(ADP-ribose) polymerase. J Pharmacol Exp Ther 2015; 353(3):446-57.

10. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res 2012; 72(21):5588-99.

11. Murai J, Huang SY, Renaud A, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. Mol Cancer Ther 2014; 13(2):433-43.

12. Hopkins TA, Shi Y, Rodriguez LE, et al. Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. Mol Cancer Res 2015; 13(11):1465-77.

13. Ioannidou A, Goulielmaki E, Garinis GA. DNA damage: from chronic inflammation to age-related deterioration. Front Genet 2016; 7:187.

14. Hartlova A, Erttmann SF, Raffi FA, et al. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. Immunity 2015; 42(2):332-43.

15. Parkes EE, Walker SM, Taggart LE, et al. Activation of STING-dependent innate immune signaling by S-phase-specific DNA damage in breast cancer. J Natl Cancer Inst 2017; 109(1):djw199.

16. Soriani A, Zingoni A, Cerboni C, et al. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood 2009; 113(15):3503-11.

17. Tang ML, Khan MK, Croxford JL, et al. The DNA damage response induces antigen presenting cell-like functions in fibroblasts. Eur J Immunol 2014; 44(4):1108-18.

18. Huang J, Wang L, Cong Z, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a BRCA1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun 2015; 463(4):551-6.

19. Study report PF-06944076_10Apr17_105548. Talazoparib Induces Immunogenicity Through an Innate Immune-mediated Mechanism.

20. Jiao S, Xia W, Yamaguchi H, et al. PARP Inhibitor Upregulates PD-L1 Expression and Enhances Cancer-Associated Immunosuppression. Clin Cancer Res 2017; 23(14):3711-20.

21. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat 2017; :16 pages.

22. Fakhrejahani F, Madan RA, Dahut WL, et al. Avelumab in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2017; 35(Suppl 15):Abstr 159.

23. Investigator's Brochure Talazoparib (PF-06944076), August 2018.

24. Litton JK, Rugo HS, Ettl J, et al. EMBRACA A phase 3 trial comparing talazoparib, an oral PARP inhibitor, to physician's choice of therapy in patients with advanced breast cancer and a germline BRCA-mutation. Oral presentation at San Antonio Breast Cancer Sypmposium, 9-5 Dec 2017. [available upon request].

25. Lee JM, Cimino-Mathews A, Peer CJ, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-Ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study. J Clin Oncol 2017; 35(19):2193-202.

26. Domcheck SM, Postel-Vinay S, Bang YJ, et al. An open-label, multitumor, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer (MBC). In: San Antonio Breast Cancer Symposium; 5-9 Dec 2017; San Antonio, TX. 2017: Abstr PD6-11.

27. Domchek SM, Aghajanian C, Shapira-Frommer R, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol 2016; 140(2):199-203.

28. RUBRACA™ (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc; 2017.

29. Konstantinopoulos PA, Sachdev JC, Schwartzberg L, et al. Dose-finding combination study of niraparib and pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC) or recurrent platinum-resistant epithelial ovarian cancer (OC). Annals of Oncology 2017; 28(Suppl 5):v406-v407.

30. Tesaro press release. Available: http://ir.tesarobio.com/news-releases/news-release-details/tesaro-summarizes-zejula-and-tsr-042-data-presented-2017-esmo Accessed: 6 Feb 2018.

31. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 376(9737):235-44.

32. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015; 33(3):244-50.

33. de Bono J, Ramanathan RK, Mina L, et al. Phase 1, dose-escalation, two-part trial of PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov 2017; 7(6):620-9.

34. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017; 377(6):523-533.

35. Brown JS, Kaye SB, Yap TA. PARP inhibitors: the race is on. Br J Cancer 2016; 114(7):713-5.

36. Connor AA, Denroche RE, Jang GH, et al. Association of Distinct Mutational Signatures With Correlates of Increased Immune Activity in Pancreatic Ductal Adenocarcinoma. JAMA Oncol 2017; 3(6):774-783.

37. Strickland KC, Howitt BE, Shukla SA, et al. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget 2016; 7(12):13587-98.

38. Green AR, Aleskandarany MA, Ali R, et al. Clinical Impact of Tumor DNA Repair Expression and T-cell Infiltration in Breast Cancers. Cancer Immunol Res 2017; 5(4):292-299.

39. PF-06944076_10Apr17_105548. Talazoparib Induces Immunogenicity Through an Innate Immune-mediated Mechanism. 10 Apr 2017.

40. PF-06944076_10Apr17_105337. Talazoparib Potentiates Therapeutic Efficacy of Immune Checkpoint Blockade Targeting the PD-1-PD-L1 Pathway. 4 Apr 2017.

41. Lord CJ, Ashworth A. Targeted therapy for cancer using PARP inhibitors. Curr Opin Pharmacol 2008; 8(4):363-9.

42. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011; 12(9):852-61.

43. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015; 373(18):1697-708.

44. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017; 18(1):75-87.

45. Karzai F, Madan RA, Owens H, et al. Combination of PDL-1 and PARP inhibition in an unselected population with metastatic castrate-resistant prostate cancer (mCRPC). J Clin Oncol 2017; 35(Suppl 15):5026.

46. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010; 28(15):2512-9.

47. Pahuja S, Appleman LJ, Belani CP, et al. Preliminary activity of veliparib (V) in BRCA2-mutated metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2015; 33(Suppl, 7):Abstr 170.

48. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013; 14(9):882-92.

49. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39(1):1-10.

50. Galluzzi L, Buque A, Kepp O, et al. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol 2017; 17(2):97-111.

51. Wang H, Hu S, Chen X, et al. cGAS is essential for the antitumor effect of immune checkpoint blockade. Proc Natl Acad Sci U S A 2017; 114(7):1637-1642.

52. Timms KM, Abkevich V, Hughes E, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. Breast Cancer Res 2014; 16(6):475.

53. Lheureux S, Lai Z, Dougherty BA, et al. Long-term responders on olaparib maintenance in high-grade serous ovarian cancer: clinical and molecular characterization. Clin Cancer Res 2017; 23(15):4086-94.

54. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016; 375(22):2154-2164.

55. Khunger M, Hernandez AV, Pasupuleti V, et al. Programmed cell death 1 (PD-1) ligant (PD-L1) expression in solid tumors as a predictive biomarker of benefit from PD-1/PD-L1 axis inhibitors: a systematic review and meta-analysis. JCO Precis Oncol 2017; 1:1-15.

56. The Cancer Genome Atlas. Available: https://cancergenome.nih.gov/.

57. Gradishar W, Johnson K, Brown K, et al. Clinical variant classification: a comparison of public databases and a commercial testing laboratory. Oncologist 2017; 22(7):797-803.

58. Yang S, Lincoln SE, Kobayashi Y, et al. Sources of discordance among germ-line variant classifications in ClinVar. Genet Med 2017; 19(10):1118-26.

59. Wang DD, Zhang SZ, Zhao H, et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009; 49(9):1012-24.

60. Gangadhar TC, Mehnert J, Patnaik A, et al. Population pharmacokinetic (popPK) model of pembrolizumab (pembro; MK-3475) in patients (pts) treated in KEYNOTE-001 and KEYNOTE-002. J Clin Oncol 2015; 33(Suppl):Abstr 3058.

61. Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab (Nivo) benefit-risk profile from a 240-mg flat dose versus a 3-mg/kg dosing regimen in patients (Pts) with solid tumors. Ann Oncol 2016; 27(Suppl 6):1098P.

62. Ganguly B, Dolfi SC, Rodriguez-Rodriguez L, et al. Role of biomarkers in the development of PARP inhibitors. Biomark Cancer 2016; 8(Suppl 1):15-25.

63. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375(19):1823-33.

64. Goodin S, Griffith N, Chen B, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. J Oncol Pract 2011; 7(1):7-12.

65. Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016; 34(12):1402-18.

66. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011; 20(10):1727-36.

67. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001; 33(5):337-43.

68. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85(5):365-76.

69. Osoba D, Aaronson N, Zee B, et al. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Life Res 1997; 6(2):103-8.

70. Cull A, Howat S, Greimel E, et al. Development of a European Organization for Research and Treatment of Cancer questionnaire module to assess the quality of life of ovarian cancer patients in clinical trials: a progress report. Eur J Cancer 2001; 37(1):47-53.

71. Greimel E, Bottomley A, Cull A, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 2003; 39(10):1402-8.

72. Sprangers MAG, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol 1996; 14(10):2756-68.

73. van Andel G, Bottomley A, Fosså SD, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008; 44(16):2418-24.

74. National Cancer Institute. Patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) item library (version 1.0). In: Bethesda, MD: National Institutes of Health; 2016: 1 page.

75. Heller G, McCormack R, Kheoh T, et al. Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: a comparison with prostate-specific antigen across five randomized phase III clinical trials. J Clin Oncol 2017; JCO2017752998.

76. Basch E, Rogak LJ, Dueck AC. Methods for Implementing and Reporting Patient-reported Outcome (PRO) Measures of Symptomatic Adverse Events in Cancer Clinical Trials. Clin Ther 2016; 38(4):821-30.

77. Goodin S, Griffith N, Chen B, et al. Safe handling of oral chemotherapeutic agents in clinical practice: recommendations from an international pharmacy panel. J Oncol Pract 2011 Jan; 7(1):7-12.

78. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; 33(28):3199-212.

79. Schleimer RP, Jacques A, Shin HS, et al. Inhibition of T cell-mediated cytotoxicity by anti-inflammatory steroids. J Immunol 1984; 132(1):266-71.

80. Khan MM. Immunosuppressive Agents. In: Immunopharmacology. New York: Springer; 2008: p. 87-105.

81. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012; 30(21):2691-7.

82. Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013; 31(14):1785-91.

83. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-55.

84. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2):228-47.

Appendix 1. Abbreviations and Definitions of Terms

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

ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
ADME	Absorption, Distribution, Metabolism, and Excretion
ADP	Adenosine Diphosphate
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATM	Ataxia-Telangiectasia Mutated
ATR	Ataxia-Telangiectasia and Rad3-Related
AUC	Area Under the Curve
BA	Biomarker Analysis
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BP	Blood Pressure
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
BRCA	BReast CAncer Gene
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CA-125	Cancer Antigen 125
CDK	Cyclin-Dependent Kinase
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
CL_{CR}	Creatinine Clearance
CL/F	Apparent Oral Clearance
C_{max}	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
C_{trough}	Lowest (trough) Concentration
CR	Complete Response
CRF	Case Report Form
CRP	C-Reactive Protein
CRPC	Castration-Resistant Prostate Cancer
CSA	Clinical Study Agreement
CSR	Clinical Study Report

CT	Computed Tomography
CTA	Clinical Trial Application
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CV	Coefficient of Variation
CYP	Cytochrome P450
D	Dose
DC	Dendritic Cell
DDI	Drug-Drug Interaction
DDR	DNA Damage Repair
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of response
DSB	Double Strand DNA Breaks
DU	Dispensable Unit
E	Escalation/Re-Escalation
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDP	Exposure During Pregnancy
EDTA	Ethylene Diamene Tetra-acetic Acid
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
ER	Estrogen Receptor
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FANC	Fanconi Anemia Complementation
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed Paraffin-Embedded
FSH	Follicle Stimulating Hormone
gBRCAm	germline Breast Cancer Gene mutation
GC/GEJ	Gastric and Gastro-esophageal Cancers
GCIG	Gynecological Cancer Intergroup
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GITR	Glucocorticoid Induced TNF Receptor
GnRH	Gonadotropin-Releasing Hormone
GMP	Good Manufacturing Procedure
GVHD	Graft Versus Host Disease
HA	Hyaluronic Acid
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus

HER2	Human Epidermal Growth Factor Receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	Hormone Receptor
HR+	Hormone Receptor Positive
HRD	Homologous Recombination Deficiency
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IASLC	International Association for the Study of Lung Cancer
ICD	Informed Consent Document
ICH	International Council for Harmonisation
ICOSL	Inducible Costimulator Ligand
ID	Identification
IDO	Indoleamine 2,3-Dioxygenase
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
INN	International Nonproprietary Name
INR	International Normalized Ratio
IP	Investigational Product
IQR	Interquartile Range
irAE	Immune-Related Adverse Event
irCR	Immune-Related Complete Response
irOR	Immune-Related Objective Response
irPD	Immune-Related Progressive Disease
irPR	Immune-Related Partial Response
irSD	Immune-Related Stable Disease
IRB	Institutional Review Board
irDR	Immune-Related Duration of Response
irORR	Immune-Related Objective Response Rate
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLQ	Lower Limit of Quantitation
LOH	Loss of Heterozygosity
LSLV	Last Subject Last Visit

mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
mCRPC	metastatic Castration Resistant Prostate Cancer
M-CSF	Macrophage-Colony Stimulating Factor
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MCC	Merkel Cell Carcinoma
MHC	Major Histocompatibility Compex
mMCC	metastatic Merkel Cell Carcinoma
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
mTPI	Modified Toxicity Probability Interval
NA	North America
N/A	Not Applicable
Nab	Neutralizing Antibody
NCI	National Cancer Institute
NE	Not Estimable
NEMO	NF-κB essential modulator
NHL	Non-Hodgkin's Lymphoma
NK	Natural Killer
NKG2DL	Natural Killer Group 2 Member D Ligand
NKT	Natural Killer T-cell
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OC	Ovarian Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PBMC	Peripheral Blood Mononuclear Cell
PCD	Primary Completion Date
PCT	Physician's Choice Therapy
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PO	Orally
PET	Positron Emission Tomography
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PMAP	Pharmacometric analysis plan
PR	Partial Response

PR	Progesterone Receptor
PRO-CTCAE	Patient Reported Outcomes - Common Terminology Criteria for Adverse Events
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog Gene
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
QD	Once Daily
RCC	Renal Cell Carcinoma
RE	Re-escalation
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic Acid
ROS1	c-Ros Oncogene 1
RP2D	Recommended Phase 2 Combination Dose
S	Stay (at current dose)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SOC	Summary of Changes
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
STING	Stimulation of Interferon Genes
$t_{1/2}$	Terminal Half-Life
TBili	Total Bilirubin
TCGA	The Cancer Genome Atlas
TCR	T-cell Receptor
TDO	Tryptophan 2,3-Dioxygenase
TE	Target Engagement
TEAE	Treatment Emergent Adverse Event
TIL	Tumor Infiltrating Lymphocytes
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time to Maximum Plasma Concentration
TNBC	Triple-Negative Breast Cancer
TO	Target Occupancy
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
TTR	Time-to-Tumor Response
UC	Urothelial Cancer
ULN	Upper Limit of Normal
UPM	Unit Probability Mass
US	United States
USPI	United States Package Insert
UTI	Urinary Tract Infection

VEGF	Vascular Endothelial Growth Factor
V/F	Apparent Volume of Distribution
V_{ss}/F	Apparent Steady-State Volume of Distribution
WBC	White Blood Cell
WT	Wild Type
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

Appendix 2. ECOG Performance Status

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

From: Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649–655.[83]

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

Adapted from E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[84]

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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

Non-measurable disease

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

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

Normal sites

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

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

RECORDING TUMOR ASSESSMENTS

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

Target Lesions

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

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

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

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

Non-target Disease

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

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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

Target Disease

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

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

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

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

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

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

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

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

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

Non-target Disease

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

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

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

- Not evaluable (NE): Progression has not been determined and one or more non-target lesion sites have not been assessed or assessment methods used were inconsistent with those used at baseline or one or more non-target lesions cannot be assessed (eg, poorly visible or unclear images) or one or more non-target lesions were excised or irradiated and have not reappeared or increased.

New Lesions

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

Supplemental Investigations

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

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

Subjective Progression

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

Determination of Tumor Response by RECIST

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

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

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

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

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/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 start of the treatment at a minimum interval of 6 weeks.

Appendix 4. Assessment of Radiographic Response and Progression in Patients with Metastatic CRPC

Radiographic imaging for patients with CRPC is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis). Bone imaging must be whole body radionuclide bone scan (scintigraphy).

The investigator will assess response of soft tissue disease by RECIST v1.1 (see Appendix 3). However, bone disease will not be considered as non-target lesions assessed by RECIST v1.1. An objective response is defined as a best overall response of CR or PR per RECIST v1.1 and must be confirmed on repeated imaging at least 4 weeks after initial documentation.

Bone disease will be assessed for progressive disease only by PCWG3.[64] The documentation required for the determination of radiographic progression is shown in the table below.

Criteria for Evidence of Radiographic Progression

Date Progression Detected[a]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 8	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: At least 6 weeks after progression identified or at Week 16 visit[b]	2 or more new bone lesions on bone scan compared to Week 8 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 16 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan	Timing: At least 6 weeks after progression identified or at next imaging time point[b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan[c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

a Progression detected by bone scan at an unscheduled visit either before Week 8 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
b Confirmation must occur at the next available scan.
c For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3. See table below for the timing of confirmatory imaging requirements.

Confirmatory Imaging Requirements for Patients with mCRPC Based on RECIST v1.1 and PCWG3

Disease Site	Response	Progression[a]
Soft tissue	Must be confirmed at least 4 weeks later	No confirmation required
Bone	Not applicable	Must be confirmed at least 6 weeks later

a To inform permanent treatment discontinuation.

Radiographic PFS is defined as the time from enrollment to documentation of radiographic progression in soft tissue by investigator' assessment according to RECIST v1.1, in bone by investigator's assessment according to PCWG3, or death, whichever occurs first.

Appendix 5. EuroQoL EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑

I have slight problems walking ❑

I have moderate problems walking ❑

I have severe problems walking ❑

I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(eg, work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN/DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

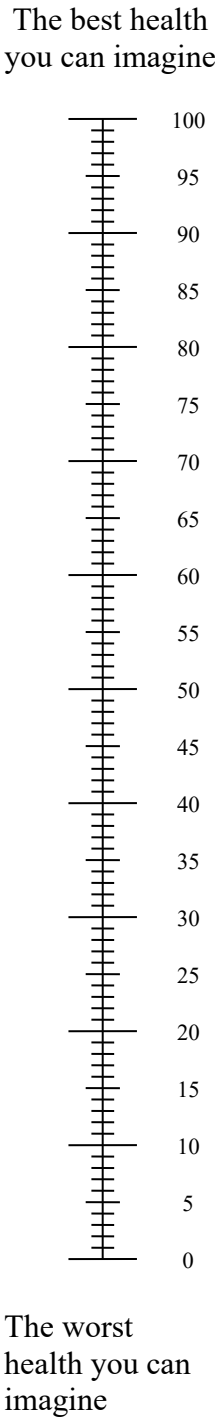
I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 6. EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

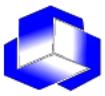
29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7. EORTC QLQ - OV28



EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you have abdominal pain?	1	2	3	4
32.	Did you have a bloated feeling in your abdomen/stomach?	1	2	3	4
33.	Did you have problems with your clothes feeling too tight?	1	2	3	4
34.	Did you experience change in bowel habit as a result of your disease or treatment?	1	2	3	4
35.	Were you troubled by passing wind/gas/flatulence?	1	2	3	4
36.	Have you felt full up too quickly after beginning to eat?	1	2	3	4
37.	Have you had indigestion or heartburn?	1	2	3	4
38.	Have you lost any hair?	1	2	3	4
39.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40.	Did food and drink taste different from usual?	1	2	3	4
41.	Have you had tingling hands or feet?	1	2	3	4
42.	Have you had numbness in your fingers or toes?	1	2	3	4
43.	Have you felt weak in your arms or legs?	1	2	3	4
44.	Did you have aches or pains in your muscles or joints?	1	2	3	4
45.	Did you have problems with hearing?	1	2	3	4
46.	Did you urinate frequently?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Have you had skin problems (eg, itchy, dry)?	1	2	3	4
48.	Did you have hot flushes?	1	2	3	4
49.	Did you have night sweats?	1	2	3	4
50.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51.	Have you been dissatisfied with your body?	1	2	3	4
52.	How much has your disease been a burden to you?	1	2	3	4
53.	How much has your treatment been a burden to you?	1	2	3	4
54.	Were you worried about your future health?	1	2	3	4

During the past 4 weeks:		Not at All	A Little	Quite a Bit	Very Much
55.	To what extent were you interested in sex?	1	2	3	4
56.	To what extent were you sexually active?	1	2	3	4
Answer the following two questions only if you were sexually active:					
57.	To what extent was sex enjoyable for you?	1	2	3	4
58.	Did you have a dry vagina during sexual activity?	1	2	3	4

Appendix 8. EORTC QLQ - BR23

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you have a dry mouth?	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4
During the past <u>four</u> weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Did you have any pain in your arm or shoulder?	1	2	3	4
48.	Did you have a swollen arm or hand?	1	2	3	4
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Was the area of your affected breast swollen?	1	2	3	4
52.	Was the area of your affected breast oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (eg, itchy, dry, flaky)?	1	2	3	4

Appendix 9. QLQ-PR25

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks…	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

Appendix 10. PRO CTCAE

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊠ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

6.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

10.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

12.	In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

13.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

14.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

15.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

16.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

17.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

18.	In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe