A PHASE 1B/2 STUDY TO EVALUATE SAFETY AND ANTI-TUMOR ACTIVITY OF AVELUMAB IN COMBINATION WITH THE POLY (ADENOSINE DIPHOSPHATE [ADP]-RIBOSE) POLYMERASE (PARP) INHIBITOR TALAZOPARIB IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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Investigational Product Number:	MSB0010718C MDV3800, BMN 673
Investigational Product Name:	Avelumab (MSB0010718C) Talazoparib (MDV3800, BMN 673)
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[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	14 June 2017	Not applicable (N/A)
Protocol Amendment 1	14 August 2017	The following changes to the original protocol were requested by the US FDA: • Inclusion criteria 1 in Section 4.1 was updated to modify the Phase 1b study population; • The DLT definition criteria in Section 3.2 were updated; • The recommended dose modification for talazoparib following Grade 3 non-hematologic toxicities has been updated in Table 5 to require dose reduction. Exceptions to the requirement for dose reductions are included. In addition, the following changes were implemented: • The secondary endpoint for PK was updated to better indicate the parameters to be reported and analyzed; • The study design schema (protocol summary and Figure 3) was updated to correct the number of patients with ovarian cancer to be enrolled in C1 and C2. Section 9.3.3 was also updated accordingly; • The information about talazoparib clinical experience in Section 1.2.2 was updated to report the updates included in the talazoparib July 2017 IB; • Several administrative changes were included to improve readability. • Changes were made to study design schema (protocol summary and Figure 3), secondary endpoints, Schedule of Activities, inclusion criteria and Sections 1.2.4, 1.2.8, and 7.4 to

Document	Version Date	Summary of Changes and Rationale
		reflect a change in the choice of assay for assessment of DDR defects. • Changes were made to the Schedule of Activities and Section 7.4.2 to reflect the addition of baseline ctDNA collection.
Protocol Amendment 2	26 January 2018	The following changes were implemented: • Addition of Cohort F and rationale to include patients with advanced solid tumors with germline or somatic defects in BRCA1, BRCA2, or ATM genes who are not eligible for Cohorts A1, A2, B1, B2, C1, C2, D, E1, or E2. • Rationale for eligibility criteria for pancreatic cancer patients in Cohort F was added. • Cohort C1 size was reduced to up to approximately 20 patients. • Inclusion criteria for all cohorts, bone marrow function, renal function, and use of P-glycoprotein inhibitors were clarified. • Coagulation tests were clarified. • Contraception methods were revised. • Tumor mutational burden in baseline tumor tissue was added as a secondary endpoint. • Exploratory endpoints were clarified. • The introduction was updated with additional preliminary data for talazoparib. • The eligibility worksheet was removed as it will not be applicable to Cohort F. • Prohibited concomitant medications and therapies and use of inhibitors of P-gp were revised.

Document	Version Date	Summary of Changes and Rationale
		• Administrative changes were included to improve readability. • Optional ctDNA collections on Day 1 of additional on-treatment cycles were added.
Protocol Amendment 3	20 November 2018	The following changes were implemented: • Human epidermal growth factor receptor 2 negative requirement was added to inclusion criterion for hormone receptor positive breast cancer patients for clarity. • Consistent with the Avelumab Investigator's Brochure (version 8, 16 May 2018), the protocol was revised to update relevant background information, and recommendation for management of Grade 1 to 2 immune-related rash was updated. • Consistent with changes implemented in the updated talazoparib Investigator's Brochure (dated August 2018), the protocol was revised to increase the duration of contraception use and concomitant medication restrictions. Relevant background pharmacokinetic information was also updated. • Based on limitations in utility of this and/or complexity to collect this exploratory endpoint, immune-related RECIST (irRECIST) assessments and any associated elements were removed or revised accordingly. • Sample size for Cohort A2 was reduced to 20 patients as the patient population has changed and this cohort is now only exploratory. • Sample size for Cohort F was reduced to 10 patients as the original intent was to bridge enrollment until study B9991032 was enrolling. That study is now open and there is

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		no longer a need to enroll 40 patients in this cohort. • Flexibility in the target number of patients to be enrolled in the Phase 2 cohorts of the study was added to avoid a dedicated protocol amendment in case additional data are needed in a specific biomarker-defined population. • The Schedule of Activities was updated to clarify procedures for patients who continue treatment beyond 2 years (Cycles >25) to lessen study participation burden for long term study participants. Serum/urine pregnancy test procedures are no longer required at Day 60 and Day 90 of Short-Term Follow-Up (only Day 30). • Prep D1 collection was clarified to only be collected on Day 1 of Cycle 1. It will not be collected on Day 1 of subsequent cycles (optional) or at end of treatment. • Physical exams are permitted to be performed 1 day prior to the scheduled visit to confirm any findings before dosing. • Permissible highly effective methods of contraception were updated as per current protocol standard, including the addition of sexual abstinence. • DDR defect status assessment procedures were revised to allow prospective and local (where applicable) testing of DDR defects. • Preliminary safety data from the Phase 1b portion of this study were added to Benefit/Risk Assessment. • Inclusion criteria for Cohort A2 were revised to allow inclusion of patients who have previously received anti-PD-1/L1 treatment.

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		• In response to queries raised by the Ministry of Food and Drug Safety of South Korea for sites in South Korea only, specific eligibility criteria were restricted for Cohorts A1, B1, and D. • A DDR gene list has been added inclusion criteria for Cohorts A2, B2, and E2, to better define the DDR defect positive status required for eligibility. • Language regarding talazoparib administration was revised to clarify procedures for any missed doses. • Requirements for tumor assessments for progressive disease confirmation were removed. • A separate withdrawal of consent form is not applicable to this study and was removed from procedures. • Activated partial thromboplastin time assessment was permitted as an alternative to partial thromboplastin time. Prothrombin time was removed. • Existing objectives for biomarker and pharmacodynamic assessments were revised and re-ordered for clarity. • Tumor tissue sample procedures were revised for clarity on prospective and/or local testing. • Editorial updates have been made for consistency and readability.

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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 inhibition 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 (MCC). 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. 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.

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. Talazoparib was approved by the FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline Breast Cancer susceptibility gene (BRCA)-mutated human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer.

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, including non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer, recurrent platinum-sensitive ovarian cancer, UC, metastatic castration-resistant prostate cancer (mCRPC), and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic (as classified by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology),[1] germline or somatic defects in -BRCA1, BRCA2, or ataxia-telangiectasia mutated (ATM) genes.

Background:

Avelumab, as a single agent, has demonstrated efficacy, as well as an acceptable toxicity profile in patients with multiple types of solid tumors, including NSCLC, breast cancer, mCRPC, UC, and ovarian cancer in Study EMR100070-001. In patients with first-line advanced NSCLC, a confirmed and unconfirmed objective response rate (ORR) of 22.4% (95% confidence interval [CI]: 16.2, 29.8) was observed, while 14.1% (95% CI: 9.4, 20.0) of second-line NSCLC patients had confirmed or unconfirmed responses (39% responded by the first assessment at 6 weeks and 73% had responded by 12 weeks). In

patients with locally advanced or metastatic UC, who were either cisplatin ineligible or had progressive disease (PD) after at least 1 line of platinum-based therapy, the confirmed ORR was 17.6% (95% CI: 10.9, 22.5). In patients with recurrent or refractory ovarian cancer who had progression within 6 months of platinum-based therapy or progression after subsequent therapy in previously relapsed patients, the ORR, based on confirmed and unconfirmed responses, was 9.7% (95% CI: 5.1, 16.3). In patients with metastatic breast cancer refractory to or progressing after standard-of-care therapy the unconfirmed ORR was 4.8% (95% CI: 2.1, 9.2); stable disease was observed in 55.6% of the patients with mCRPC.

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, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001. In patients with advanced breast cancer, an ORR of 44.4% (8 of 18; 95% CI: 21.5, 69.2) was observed. In patients with advanced ovarian/peritoneal cancer, an ORR of 48.0% (12 of 25; 95% CI: 27.8, 68.7) was observed. Only 1 patient with prostate cancer was treated in this study and that patient did not have an objective response. In a Phase 3 trial in patients with BRCA 1/2 positive locally advanced and/or metastatic breast cancer (protocol no. 673-301 [EMBRACA]), single-agent talazoparib demonstrated superior progression-free survival (PFS) versus physician choice chemotherapy.[1]

Talazoparib is proposed for evaluation in combination with avelumab in patients with locally advanced (primary or recurrent) or metastatic solid tumors based on the acceptable safety and pharmacokinetic (PK) profiles observed for each of the investigational products when administered as single agents. Preliminary clinical activity has been observed for these investigational products, or an agent of the same class, in the tumor types to be evaluated. Furthermore, the proposed complementary mechanisms of action of avelumab and talazoparib may lead to increased anti-tumor activity. 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. Talazoparib, via its ability to promote increased DNA damage, has the potential to promote several of these key stages of the immune response. Specifically, 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. This expectation is further supported by preclinical studies in syngeneic mouse models of ovarian and colorectal cancer, which

demonstrate 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.

The primary purpose of this study is to assess the safety and early signs of efficacy of the avelumab and talazoparib combination in patients with locally advanced (primary or recurrent) or metastatic solid tumors, including NSCLC, TNBC, HR+/HER2- breast cancer, recurrent platinum-sensitive ovarian cancer, UC, mCRPC, and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic, germline or somatic defects in BRCA1, BRCA2, or ATM genes. These tumor types were selected on the basis that one of the investigational products, or an agent of the same class, has shown preliminary clinical activity in the tumor type of interest or because the tumor types are expected to have a high prevalence (≥35%) of biomarkers indicating increased sensitivity to talazoparib-mediated DNA damage. In the setting of NSCLC, early signs of efficacy will be assessed in anti-PD-1/L1 naïve patients and also in a cohort of patients who have previously received anti-PD-1/L1 treatment, in order to assess the ability of the combination to overcome resistance to anti-PD-L1 treatment in this setting. It is anticipated that patients with an increased sensitivity to talazoparib will be most likely to respond to the combination treatment, independent of their tumor type. In order to test this hypothesis, two potential biomarkers of talazoparib sensitivity (genomic scarring measured via a loss of heterozygosity [LOH] and presence of defects in a panel of DNA damage repair [DDR] genes) will be evaluated prospectively or retrospectively using the Foundation One assay in all cohorts.

The BRCA1, BRCA2, and ATM genes represent some of the DDR genes with the greatest amount of data supporting their ability to confer sensitivity to PARP inhibitors.[3] Given the greater confidence in these 3 DDR genes as predictive biomarkers, they will be assessed in prospectively selected cohorts of patients. Cohort C2, will constitute patients with ovarian cancer who have previously identified pathogenic, or likely pathogenic, germline or somatic defects in either BRCA1 or BRCA2 genes. Cohort F will constitute patients with locally advanced (primary or recurrent) or metastatic solid tumors, independent of tissue of origin, with previously identified pathogenic, or likely pathogenic, germline or somatic defects in BRCA1, BRCA2, or ATM genes.

Study Objectives and Endpoints:

Primary Objectives

- Phase 1b: To assess the Dose-Limiting Toxicity (DLT) rate of avelumab in combination with talazoparib in patients with locally advanced or metastatic solid tumors in order to select the recommended Phase 2 dose (RP2D) of talazoparib for the combination.

- Phase 2: To assess ORR of avelumab in combination with talazoparib, as assessed by the Investigator, per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) in patients with locally advanced or metastatic solid tumors and per RECIST v1.1 and Prostate Cancer Working Group 3 (PCWG3) in patients with mCRPC.

Secondary Objectives

- 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 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, tumor mutational burden (TMB; defined as the total number of mutations in the tumor genome, or number of mutations per megabase of DNA if derived from targeted sequencing),[4] and potential biomarkers of PARP inhibitor sensitivity in baseline tumor tissue.

[redacted]

Primary Endpoints

- Phase 1b: DLT during the DLT evaluation period (Cycle 1).
- Phase 2: Confirmed objective response (OR), as assessed by the Investigator using RECIST v1.1 in patients with locally advanced or metastatic solid tumors (see Appendix 3) and RECIST v1.1 and PCWG3 in patients with mCRPC (see Appendix 5).

Secondary Endpoints

- Adverse events (AEs) as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for AEs [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 for avelumab and talazoparib including: pre-dose/trough concentrations (C_{trough}) and post-dose concentrations (for talazoparib) or maximum concentrations (C_{max}) for avelumab.

- Avelumab anti-drug antibody (ADA) levels and neutralizing antibodies (Nab) against avelumab.

- Phase 1b: Confirmed OR, as assessed by the Investigator using RECIST v1.1 in patients with locally advanced or metastatic solid tumors and RECIST v1.1 and PCWG3 in patients with mCRPC.

- Phase 1b and Phase 2: Time-to-event endpoints including time to tumor response (TTR), duration of response (DR), and progression-free survival (PFS) as assessed by the Investigator using RECIST v1.1 for patients with solid tumors and using RECIST v1.1 and PCWG3 for patients with mCRPC, time to prostate-specific antigen (PSA) progression for patients with mCRPC, and OS.

- PSA response ≥50% for patients with mCRPC.

- Cancer antigen (CA)-125 response for patients with ovarian cancer.

- PD-L1 expression level in baseline tumor tissue.

- TMB in baseline tumor tissue.

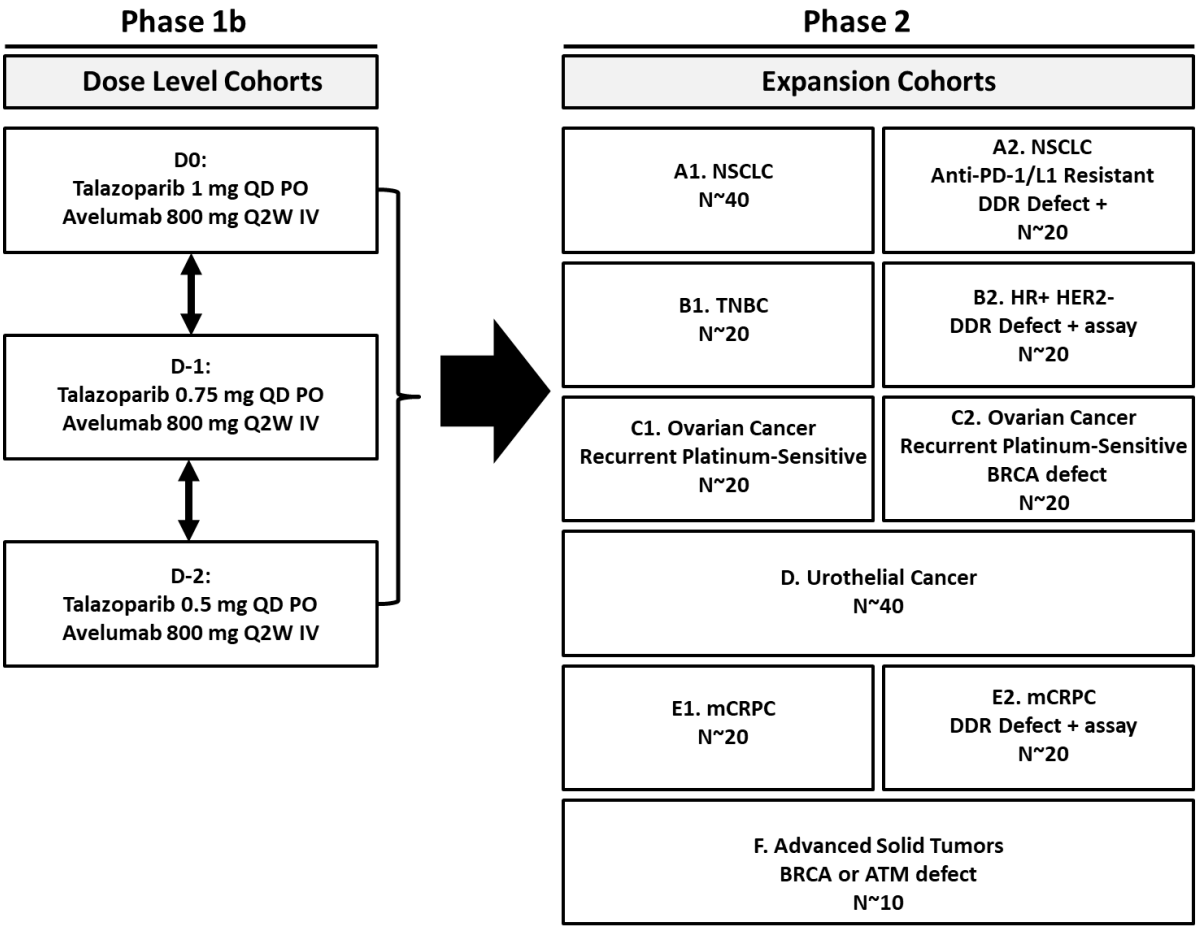
- Genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue.

[redacted]

[redacted]

Study Design:

The study design and specific expansion cohorts, including the number of patients to be enrolled into each cohort, are shown below. Approximately 242 patients in total will be enrolled into the study.



ATM= ataxia telangiectasia mutated; BC= breast cancer; BRCA=BReast CAncer susceptibility gene; mCRPC= metastatic castration-resistant prostate cancer; D=Dose; HER2-=human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; DDR=DNA damage repair; DDR Defect +=DDR defect positive as determined by the Foundation One assay or validated local assay result; IV=intravenous; NSCLC=non-small cell lung cancer; PD-L1= Programmed Death-Ligand 1; PO= orally; Q2W=every 2 weeks; QD=every day; TNBC= triple-negative breast cancer; TPS= tumor proportion score.

[redacted]

Phase 1b

During the Phase 1b portion of this study, patients with locally advanced or metastatic solid tumors, who meet eligibility criteria, will be treated with one of up to 3 different doses of talazoparib (0.5 mg, 0.75 mg, or 1.0 mg) administered orally every day (QD) in combination with a fixed dose of avelumab 800 mg intravenous (IV) every 2 weeks (Q2W), and will be evaluated for DLTs. The modified toxicity probability interval (mTPI) method will be used to identify the RP2D for talazoparib (see Appendix 4). The avelumab and talazoparib combination will be administered in 28-day cycles. The DLT evaluation period will be 28 days (ie, Cycle 1). The target enrollment cohort size is 3-6 patients.

The starting dose level will be 1.0 mg talazoparib QD plus 800 mg avelumab Q2W. For patients with moderate renal impairment (CrCl 30-59 mL/min), the 1 mg QD talazoparib starting dose should be reduced to 0.75 mg QD (Section 1.2.6.2). The dose levels of the combination to be evaluated are included in the table below.

Dose Level	Talazoparib Dose (Oral)	Avelumab Dose (IV)
D0	1 mg QD	800 mg Q2W
D-1	0.75 mg QD	800 mg Q2W
D-2	0.5 mg QD	800 mg Q2W

D=dose; QD=once daily; Q2W=every 2 weeks

Starting with dose level D0, 3 patients will be enrolled, treated, and monitored during the 28-day DLT evaluation period. The mTPI method recommends the dose level for the next enrollment cohort of patients based on the number of DLT-evaluable patients treated at the current dose level that have reported DLTs. See Section 3.1.1.1 and Appendix 4 for Detailed Dose Escalation/De-Escalation Scheme.

When all the DLT-evaluable patients treated in a given enrollment cohort have been evaluated for DLTs during the DLT observation period (28 days; Cycle 1) or experienced a DLT, whichever comes first, the patients in the next enrollment cohort will receive the dose level of the combination as assigned by the mTPI design. As an example, if the total number of DLT-evaluable patients (cumulative in Phase 1b from prior and current cohorts) treated at the current dose combination is 3, the dose escalation/de-escalation rules are described below:

- 0 DLT in 3 DLT-evaluable patients → escalate, if a higher dose level is available;
- 1 DLT in 3 DLT-evaluable patients → remain at the same dose level;
- 2 DLTs in 3 DLT-evaluable patients → de-escalate, if a lower dose level is available and allow for possible re-escalation;
- 3 DLTs in 3 DLT-evaluable patients → de-escalate, if a lower dose level is available and consider current dose as intolerable.

In Phase 1b, patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of the investigational products in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. Additional patients will be enrolled in the specific cohort to replace patients who are not considered DLT-evaluable.

Phase 1b portion is completed when at least 12 DLT-evaluable patients have been treated at the highest dose associated with DLT rate <0.33 (see Section 9.2). Early completion of Phase 1b can be reached when 9 or more DLT-evaluable patients have been treated at the same dose level with no occurrence of DLT, as the DLT rate of <0.33 will be met.

Once the Phase 1b portion is completed and the RP2D of the combination is determined, the Phase 2 portion will be initiated.

Approximately 12-36 patients are expected to be enrolled in Phase 1b using the mTPI method.

If dose level D-2 is not tolerable, the study will be stopped and no dose combination will be further evaluated.

Phase 1b was completed in May 2018 with 12 patients enrolled.

Phase 2

The overall available data (including safety and preliminary anti-tumor activity) emerging from Phase 1b portion of the study will be evaluated before starting enrollment of patients in the Phase 2 portion of the study. The Phase 2 portion of this study will further assess the safety and preliminary anti-tumor activity of the avelumab and talazoparib combination at the RP2D. Phase 2 expansion cohorts will include patients with locally advanced (primary or recurrent) or metastatic NSCLC, TNBC, HR+/HER2- breast cancer, recurrent platinum-sensitive ovarian cancer, UC, mCRPC, and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic, germline or somatic defects in BRCA1, BRCA2, or ATM genes.

Approximately 230 patients are expected to be enrolled in Phase 2.

A given cohort size may be expanded by a limited number of additional patients (approximately 10) per Sponsor's discretion subsequent to the identification of any early signal of clinical activity that may emerge from the generated data in a biomarker-defined population.

Study Treatments:

All patients enrolled will receive avelumab and talazoparib.

Avelumab will be administered as a 1-hour IV infusion Q2W on Days 1 and 15 of each 28-day cycle at a dose of 800 mg in both Phase 1b and Phase 2.

Talazoparib will be self-administered orally once daily at 0.5 mg, 0.75 mg, or 1 mg during Phase 1b, where DLTs will be assessed during Cycle 1 and dose escalation/de-escalation will follow the mTPI design. Once the RP2D is determined in Phase 1b, the Phase 2 expansion cohorts will start enrolling at the RP2D dose of talazoparib in combination with avelumab 800 mg IV Q2W (as specified above).

In May 2018, the RP2D for talazoparib administered orally in combination with avelumab 800 mg IV Q2W was confirmed to be 1 mg QD. The talazoparib starting dose for patients with moderate renal impairment (CrCl 30-59 mL/min) will be reduced to 0.75 mg QD as discussed in the talazoparib IB.[12]

Avelumab will be administered at the investigational site on an outpatient basis. On days when both drugs are administered, talazoparib will be administered first, followed by initiation of the avelumab infusion 800 mg as a 1-hour IV infusion starting 30-60 minutes after the mandatory premedication is administered.

Statistical Methods:

The primary endpoint for Phase 2 is confirmed OR using RECIST v1.1 in patients with locally advanced or metastatic solid tumors and using RECIST v1.1 and PCWG3 in patients with mCRPC. OR is defined as a complete response (CR) or partial response (PR) per RECIST v1.1 by Investigator 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 treated patients with confirmed CR or PR per Investigator's assessment according to RECIST v1.1.

In patients with mCRPC, OR is defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST v1.1 by Investigator 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 repeated computed tomography (CT) or magnetic resonance imaging (MRI) with no evidence of confirmed bone disease progression per PCWG3 criteria by Investigator.

It is expected that 12-36 patients will need to be enrolled in Phase 1b using the mTPI design. Phase 2 expansion cohorts may each enroll up to approximately 20 or 40 patients, depending on the tumor type, as shown in the study design figure above.

In cohorts with 10, 20, and 40 treated patients, ORR can be estimated with a standard error not exceeding 0.158, 0.112, and 0.079, respectively. Within each cohort, ORR will be estimated and the 2-sided exact 90% and 95% CIs will be calculated.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the ASSESSMENTS section of the protocol for detailed information on each 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.

This schedule of activities will be followed for the entire study, including Phase 1b and Phase 2 portions. Further details can be found in Sections 5, 6 and 7.

Table 1. Schedule of Activities: Safety and Efficacy Assessments (Phases 1b and 2)

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)								Post Treatment			
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		Cycles ≥25		End of Treatment[26]	Short-Term Follow-Up[29]		Long-Term Follow-Up (Every 12 weeks)[30]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15		Day 30 after last dose	Days 60 and 90 after last dose	
Visit Window (Days)			±2	±2	±2	±2	±2	±3	±3	+7	±3	±3	±14
Informed Consent[1]	X												
Tumor History[2]	X												
Medical History[3]	X												
Baseline Signs and Symptoms[4]		X											
Height	X												
Weight	X	X		X		X				X			
Contraception Check[5]	X	X		X		X				X	X	X	X
Laboratory and Safety Assessments – Must be performed pre-dose during the Treatment Period													
Physical Examination[6]	X	X		X		X		As clinically indicated		X	X	As clinically indicated	
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	As clinically indicated	
ECOG Performance Status[8]	X	X		X		X		X	X	X	X	As clinically indicated	
Hematology[9]	X	X[24]	X	X	X	X	X	X	X	X	X	As clinically indicated	
Blood Chemistry[9]	X	X[24]	X	X	X	X	X	X	X	X	X	As clinically indicated	
Coagulation[9]	X	X[24]	As clinically indicated							X	X	As clinically indicated	
Urinalysis[10]	X	X[24]	As clinically indicated							X			
Serum/Urine Pregnancy Test (*for women of childbearing potential only*)[11]	X	X		X		X		X		X	X		
Hepatitis B and Hepatitis C Virus tests[12]	X												

Table 1. Schedule of Activities: Safety and Efficacy Assessments (Phases 1b and 2)

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)								Post Treatment			
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		Cycles ≥25		End of Treatment[26]	Short-Term Follow-Up[29]		Long-Term Follow-Up (Every 12 weeks)[30]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15		Day 30 after last dose	Days 60 and 90 after last dose	
Visit Window (Days)			±2	±2	±2	±2	±2	±3	±3	+7	±3	±3	±14
ACTH and Thyroid Function Tests[9]	X					Every 3 cycles (Cycles 3, 6, 9, etc)				X	X	X	
Testosterone *(for mCRPC patients only)*	X Results required for eligibility criteria prior to enrollment												
Triplicate 12-Lead ECG[13]	X	X[25]				Cycle 3 only[25]				X		As clinically indicated	
Enrollment and Treatment													
Enrollment[14]		X											
Talazoparib Administration[15]		QD											
Premedication for Avelumab[16]		X		X	X	X	Optional Administration, at PI discretion, based on presence/severity of prior infusion reactions						
Avelumab Administration[17]		X		X	X	X	X	X	X	X			
Tumor Assessments *(for all tumor types except mCRPC)*[18]	X	Every 8 weeks (±7 days) after C1D1. After 1 year from C1D1, every 16 weeks (±7 days) until progressive disease.								X[27]	Every 8 weeks (±7 days) after C1D1. After 1 year from C1D1, every 16 weeks (±7 days) until progressive disease.		
Tumor Assessments for *m*CRPC patients ONLY[19]	X	Every 8 weeks (±7 days) after C1D1. After 24 weeks from C1D1, every 12 weeks (±7 days) until progressive disease.								X[27]	Every 8 weeks (±7 days) after C1D1. After 24 weeks from C1D1, every 12 weeks (±7 days) until progressive disease.		

Table 1. Schedule of Activities: Safety and Efficacy Assessments (Phases 1b and 2)

Protocol Activities	Screening	Treatment Period (1 Cycle =28 Days)								Post Treatment			
	≤28 Days Prior to Enrollment	Cycle 1		Cycle 2		Cycles ≥3		Cycles ≥25		End of Treatment[26]	Short-Term Follow-Up[29]		Long-Term Follow-Up (Every 12 weeks)[30]
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15		Day 30 after last dose	Days 60 and 90 after last dose	
Visit Window (Days)			±2	±2	±2	±2	±2	±3	±3	+7	±3	±3	±14
CA-125 Tumor Marker Blood Test (*for ovarian cancer patients ONLY*)	X	X[24]		X		X				X			
PSA Tumor Marker Blood Test (*for mCRPC patients ONLY*)	X	X[24]		X		X				X			
Other Clinical Assessments													
Serious and Non-Serious Adverse Event Monitoring[20]	X	Monitored and recorded continually								X	X[28]	X[28]	
Concomitant Treatments[21]	X	Monitored and recorded continually								X	X	X	
Subsequent Anti-Cancer Treatment[22]											X	X	X
Survival[23]													X

ACTH=adrenocorticotropic hormone, C=Cycle; C1D1=Cycle 1 Day 1; CA-125=Cancer antigen 125; mCRPC=metastatic castration-resistant prostate cancer; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; FFPE=formalin-fixed paraffin-embedded; PI=Principal Investigator; PSA=prostate-specific antigen; QD=once daily.

Footnotes for Safety and Efficacy Assessments (Phases 1b and 2) 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:** Includes oncology history, information on prior regimens (duration of administration, best overall response [BOR] observed, and recurrence date), surgery, and radiation therapy.
3. **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. **Baseline Signs and Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to enrollment and record on the Medical History case report form (CRF) page.
5. **Contraception Check:** Investigator to confirm correct use of highly effective contraception, as applicable and for the duration as detailed in Sections 4.3 and 7.1.2.
6. **Physical Examination:** Physical exam may be performed up to 1 day prior to visit.
7. **Vital Signs:** Record blood pressure (BP), pulse heart rate (HR), and temperature.
8. **ECOG Performance Status:** See Appendix 2 for the criteria to assign the ECOG Performance Status at each time point.
9. **Hematology, Coagulation, Blood Chemistry, ACTH, and Thyroid Function Tests:** Hematology and blood chemistry tests may be performed up to 3 days prior to visits on Days 1 and 15 of each 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.

10. **Urinalysis:** Dipstick is acceptable. Perform microscopic analyses if dipstick is positive for blood or protein. See Section7.1.4.
11. **Serum/Urine Pregnancy Test (*for women of childbearing potential only*):** See Section 4.1 for criteria defining women of childbearing potential, as those patients require pregnancy testing. Serum or urine pregnancy tests must have sensitivity of at least 25 mIU/mL. Additionally perform pregnancy tests whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. See Section 7.1.1 for additional pregnancy testing details.
12. **Hepatitis B and Hepatitis C Virus tests:** Includes HBV surface antigen and anti-HCV antibody tests. If anti-HCV antibody test is positive, HCV RNA test must be to be performed.
13. **Triplicate 12-Lead ECG:** See Section 7.1.6 for details regarding ECGs and the procedure to follow if mean QTc is prolonged (>500 msec). If the patient experiences any cardiac AE or syncope, dizziness, seizures, or stroke, triplicate ECGs should be obtained at the time of the event.
14. **Enrollment:** Managed by an Interactive Response Technology (IRT) system operated by Pfizer Inc. See Section 5.1 for information regarding the IRT system. Investigational product administration must begin within 3 days after enrollment.
15. **Talazoparib Administration:** See Section 5.4.2 for details on talazoparib administration. On Day 1 and Day 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.
16. **Premedication for Avelumab:** An antihistamine and paracetamol (acetaminophen) must be administered approximately 30-60 minutes prior to the first 4 avelumab infusions (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). See Section 5.4.3 for further details on the premedication and Section 5.4.1 on the administration of the study combination treatment.
17. **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.
18. **Tumor Assessments (*for all tumor types except mCRPC*):** See Section 7.6 for details on tumor assessments, including tumor assessments to confirm CR or PR using RECIST version 1.1 (See Appendix 3). 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. If bone metastases are present at baseline (Screening), then repeat bone imaging is required every 16 weeks during the first year of study treatment and every 24 weeks thereafter).
19. **Tumor Assessments for mCRPC patients ONLY:** See Section 7.6.1 for details on mCRPC tumor assessments, including timing of tumor assessments to confirm CR or PR using RECIST v1.1 (See Appendix 3) or to confirm PD using PCWG3 (See Appendix 5) and the documentation required for the determination of radiographic progression. Brain imaging is 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. Bone imaging is required every 8 weeks during the first 24 weeks of study treatment and every 12 weeks thereafter.
20. **Serious and Non-Serious Adverse Event Monitoring:** AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v.4.03. 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 through and including a minimum of 90 calendar days after the last investigational product administration. If the patient begins a new anti-cancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
21. **Concomitant Treatments:** Includes all medications and non-drug supportive interventions (eg, transfusions) from 28 days prior to the start of study treatment and up to 90 days after the last dose of investigational products. If a patient begins a new anti-cancer therapy, reporting of concomitant medications should end at the time the new treatment is started. See Section 5.7 for additional details, and Section 5.7.10 for prohibited medications, which should be discussed with the patient and appropriately managed.
22. **Subsequent Anti-Cancer Treatment:** Subsequent anti-cancer therapy will be documented and recorded.

23. **Survival:** Contact patients via telephone or at the clinic for survival status independently of time of disease progression until for at least 2 years after enrollment of the last patient until death, lost-to-follow-up, patient withdrawal of consent, or study discontinued by the Sponsor, whichever comes first. For those patients without evidence of disease progression at the time of treatment discontinuation who continue to be followed with tumor assessments at Long-Term Follow-Up, survival status will be collected at the time of the scheduled tumor assessments.
24. **Hematology, Coagulation, Blood Chemistry, Urinalysis, PSA, and CA125:** It is not necessary to repeat on Cycle 1 Day 1 (C1D1) if performed within 7 days prior to C1D1 as part of Screening.
25. **Triplicate 12-Lead ECG (Day 1 Cycle 1 and Cycle 3):** Triplicate ECGs will be performed before administration of talazoparib and at the end of avelumab infusion.
26. **End of Treatment:** Perform tests/procedures if not completed during the previous 7 days.
27. **End of Treatment Tumor Assessments:** Tumor assessments should be repeated at the End of Treatment (EOT) visit if not done in the previous 4 weeks and the prior response is other than confirmed PD.
28. **Short-term Follow-up Serious and Non-Serious Adverse Event Monitoring:** Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected.
29. **Short-Term Follow-up:** All patients will be followed for safety Day 30 after last dose (±3 days) through 90 days (Day 30 via a site visit, Day 60 and Day 90 via a site visit or via phone call) after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first. A subsequent site visit may be requested if any concerns are noted during a phone call visit. 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. Laboratory assessments may be performed as clinically indicated.
30. **Long-Term Follow-up:** Follow-Up to continue until death unless lost to follow-up, consent withdrawal, or study discontinued by the Sponsor. 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 the patient was still on therapy, regardless if the patient starts a new anti-cancer therapy.

Table 2. Schedule of Activities: Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments (Phases 1b and 2)

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)			±2	±2	±2	±2	±2	+7	±3	±14
-DDR Defect Status (*for NSCLC Cohort A2, Breast Cancer Cohort B2 and Prostate Cancer Cohort E2 ONLY*)[1]	X Results required for eligibility criteria prior to enrollment									
BRCA Status (*for ovarian cancer Cohort C2 ONLY*)[2]	X Results required for eligibility criteria prior to enrollment									
ATM or BRCA Status *(for Solid Tumor Cohort F)*[3]	X Results required for eligibility criteria prior to enrollment									
DDR Defect sample on FFPE tissue for all patients[4]	X									
Blood Draw for DNA Analysis[5]		X								
Blood Draw for Talazoparib PK[6]		X	X	X		Cycles 3-4 only				
Blood Draw for Avelumab PK[7]		X	X	X		Cycles 3-4, 6, 9, 12, 18, and 24 only				
Blood Draw for Immunogenicity (ADA) Testing[8]		X	X	X		Cycles 3-4, 6, 9, 12, 18, and 24 only		X		
Genomic Banked Biospecimen Prep D1[9]		X								
Blood (plasma) for circulating tumor (ct)DNA analysis[10]		X		X (optional)		X (optional)		X		
Blood (Plasma) for Biomarker/Proteomic/ Metabolomic Analysis[11]	X		X			Cycle 3 only		X		

Table 2. Schedule of Activities: Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments (Phases 1b and 2)

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)			±2	±2	±2	±2	±2	+7	±3	±14
Blood (Serum) for Biomarker/Proteomic/ Metabolomic Analysis[12]	X	X	X			Cycle 3 only		X		
Blood Draw for TCR Analysis[13]	X	X	X			Cycle 3 only		X		
Blood Draw for RNA analysis[14]	X	X	X			Cycle 3 only		X		
Tumor Biopsy/Tissue	X[15]	Optional[16]						X[17]		

ADA=anti-drug antibodies; ATM=ataxia-telangiectasia mutated; BRCA=BReast CAncer susceptibility gene; C=Cycle; C1D1=Cycle 1 Day 1; ctDNA=circulating tumor DNA; DNA=deoxyribonucleic acid; FFPE=formalin-fixed paraffin-embedded; DDR=DNA damage repair; NSCLC=non-small cell lung cancer; PD-L1=Programmed Death-Ligand 1; PI=Principal Investigator; PK=pharmacokinetics; PSA=prostate-specific antigen; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; RNA=ribonucleic acid; TCR=T-cell receptor; TPS=tumor proportion score.

Footnotes for Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments (Phases 1b and 2) 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. **Known DDR Defect Status (*for NSCLC Cohort A2, HR+/HER2- Breast Cancer Cohort B2, and mCRPC Cohort E2 ONLY*):** For patients being screened for enrollment into cohorts A2, B2 or E2, a defect in one of 34 DDR genes, as described in Section 4.1, must have been previously documented through local laboratory testing using a tissue based next generation sequencing test performed in a CAP/CLIA-certified (or comparable local or regional certification) laboratory or using one of the approved germline tests, as described in Section 4.1. If DDR status has not been previously determined then tissue, as described in Section 7.4.1.1, must be sent for prospective DDR testing at the Foundation Medicine central laboratory no more than 45 days prior to enrollment.
2. **BRCA Status (*for ovarian cancer Cohort C2 ONLY*):** For patients to be eligible for enrollment into the ovarian cohort for tumors with a BRCA defect (Cohort C2), patients must have a previous BRCA test result demonstrating that the patient has a germline or somatic BRCA1 or BRCA2 gene defect. The test result must have been obtained by one of the approved tests. See Section 4.1.
3. **ATM or BRCA Status (*for solid tumor Cohort F ONLY*):** For patients to be eligible for enrollment into the solid tumor cohort for tumors with an ATM, BRCA1, or BRCA2 defect (Cohort F), patients must have a previous ATM, BRCA1, or BRCA2 test result demonstrating that the patient has a germline or somatic ATM, BRCA1, or BRCA2 defect, respectively. The test result must have been obtained by one of the approved tests. See Section 4.1.
4. **DDR Defect sample on FFPE tissue:** All patients in all cohorts must submit FFPE tumor tissue to the Foundation Medicine central laboratory for testing using the Foundation One assay-, as described in Section 7.4.1.1.
5. **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.

6. **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 Cycles 2-4. See Section 7.2.2.
7. **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 2-4, 6, 9,12, 18, and 24. See Section 7.2.1.
8. **Blood Draw for Avelumab Immunogenicity (ADA) Testing:** Blood samples (3.5-mL whole blood) for avelumab immunogenicity testing will be collected pre-dose (within 2 hours of talazoparib dose) on Day 1 and Day 15 of Cycles 1, on Day 1 of Cycle 2-4 and then on Day 1 of Cycles 6, 9, 12, 18, 24, and at the EOT. See Section 7.3.
9. **Genomic Banked Biospecimen Prep D1**: A 4-mL 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.
10. **Blood (plasma) for ctDNA:** A 20 mL blood specimen will be collected on Day 1 of Cycle 1 and at end of treatment. Optional ctDNA collections may be made on Day 1 of additional on-treatment cycles, for those patients also providing on-treatment biopsies. See Section 7.4.2.
11. **Blood (plasma) for Biomarker/Proteomic/Metabolomic Analysis**: A 4-mL blood biospecimen will be collected at screening then prior to dosing on Day 15 of Cycle 1, Day 1 of Cycle 3, and at EOT. See Section 7.4.2.
12. **Blood (serum) for Biomarker/Proteomic/Metabolomic Analysis**: A 10-mL blood biospecimen will be collected at screening, and then prior to dosing on Days 1 and 15 of Cycle 1, Day 1 of Cycle 3, and at EOT. See Section 7.4.2.
13. **Blood Draw for TCR Sequencing Analysis:** A 6-mL whole blood sample will be collected into a tube optimized for deoxyribonucleic acid (DNA) preservation at screening, then prior to dosing on Days 1 and 15 of Cycle 1, Day 1 of Cycle 3, and at EOT. See Section 7.4.2.
14. **Blood Draw for RNA Analysis**: Two 2.5-mL whole blood samples will be collected in designated tube to optimize sample for RNA analysis at screening, then prior to dosing on Days 1 and 15 of Cycle 1, Day 1 of Cycle 3, and at EOT. See Section 7.4.2.
15. **Tumor Biopsy/Tissue:** All patients must submit FFPE tumor tissue as described in Section 7.4.1.
16. **Tumor Biopsy during Treatment Period (Optional):** Optional biopsies are encouraged between Cycle 1 Day 15 and Cycle 3 Day 1. In addition, 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 7.4.1.3.
17. **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 poses an unacceptable risk to patients in the clinical research setting.

1. INTRODUCTION

This is a Phase 1b/2 study to evaluate safety and anti-tumor activity of avelumab (MSB0010718C), a programmed death-ligand 1 (PD-L1) specific monoclonal antibody (mAb), in combination with talazoparib (MDV3800, BMN 673), a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, in patients with locally advanced (primary or recurrent) or metastatic solid tumors, including non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer, recurrent platinum-sensitive ovarian cancer, urothelial cancer (UC), metastatic castration-resistant prostate cancer (mCRPC), and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic (as classified by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology),[1] germline or somatic defects in BReast CAncer susceptibility gene (BRCA)-1, BRCA2, or ataxia-telangiectasia mutated (ATM) genes.

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). 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.[5,6] For complete details of the in vitro and nonclinical studies, refer to the avelumab Investigator's Brochure (IB).[7]

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 (MCC) followed by approvals in Japan, Australia, European Union, Switzerland, and Israel. 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. In January 2018, avelumab was approved for the same indication in Israel.

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.

Additional information for avelumab may be found in the single reference safety document (SRSD), which for this study is the avelumab IB.[7]

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.[8,9,10] 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.[9,11]

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,[19] suggesting that this may represent a means by which tumors function to inhibit talazoparib-mediated anti-tumor immunity.

Talazoparib was approved by the FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer.

Additional information for talazoparib may be found in the SRSD, which for this study is the talazoparib IB.[12]

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.

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 metastatic MCC 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, 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 MCC (N=88). Study EMR100070-001 consists of 2 parts, a dose escalation phase and a dose expansion phase, which is performed in selected tumor types.

As of 09 June 2016, 53 patients, 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, mCRPC, 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 MCC.

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

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

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

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

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

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

A total of 244 patients (14.0%) permanently discontinued avelumab treatment due to TEAEs, including 107 patients (6.2%) discontinuing because of treatment-related TEAEs. The most frequent treatment-related TEAEs leading to treatment discontinuation were infusion-related reaction (1.8%), GGT increased (0.4%), and diarrhea, fatigue, autoimmune disorder, alanine aminotransferase (ALT) increased, blood creatine phosphokinase 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 (AEs) 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 subjects from Studies EMR100070-001 and EMR100070-003 treated with 10 mg/kg of avelumab Q2W and who had at least one valid anti-drug antibody (ADA) result as of the data cut-off date of 09 June 2016. Of the 1738 patients treated with avelumab, 1558 were evaluable for treatment-emergent ADAs and 64 (4.1%) tested positive. Titers were generally low across ADA ever-positive subjects, with no clear relationship between the duration of immunogenicity response and the maximum observed titer. Current data suggest there is no clinically meaningful impact of ADA positivity on the pharmacokinetics (PK), efficacy, or safety of avelumab.

1.2.1.1. Clinical Experience in Patients with NSCLC

1.2.1.1.1. First-Line NSCLC Patients

Study EMR 100070-001 evaluated avelumab in first-line NSCLC patients in a tumor-specific expansion cohort. As of 19 February 2016, 156 patients with advanced NSCLC not previously treated systemically for metastatic or recurrent disease, without an activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, and not preselected for PD-L1 expression, were enrolled in this cohort. The majority of subjects were Eastern Cooperative Oncology Group (ECOG) performance status 1 (69.2%), and tumor histology was adenocarcinoma (66.0%) or squamous (28.8%) in most subjects.

The objective response rate (ORR) based on confirmed and unconfirmed responses was 22.4% (95% CI: 16.2, 29.8; 35 [2 complete responses (CRs) and 33 partial responses (PRs)] of 156 patients). Responses were confirmed in 26 subjects (16.7%) at the time of data cut-off. In 24 of 35 responders (68.6%), the responses were ongoing at the time of the data cutoff. The onset of the response was rapid, with 28 of 35 responders (80%) having their first documented response by the first or second tumor assessments (Weeks 6 and 12, respectively). An additional 67 patients (42.9%) had a best overall response (BOR) of stable disease (SD). The ORR in patients with squamous cell carcinoma and adenocarcinoma was 24.4% (95% CI: 12.9, 39.5) and 22.3% (95% CI: 14.7, 31.6), respectively. An objective response was observed in 19 of 88 patients (21.6%; 95% CI: 13.5, 31.6) who had at least 1% PD-L1 positive tumor cells compared with 2 of 23 patients (8.7%; 95% CI: 1.1, 28.0) who had less than 1% PD-L1 positive tumor cells.

The median progression-free survival (PFS) as per the Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 was 17.6 weeks (95% CI: 11.6, 23.6). The Kaplan-Meier PFS rate at 24 weeks was 37.2% (95% CI: 28.6, 45.7).

1.2.1.1.2. Second-Line or Higher NSCLC Patients

Study EMR 100070-001 evaluated avelumab in second-line NSCLC patients in a tumor-specific expansion cohort. As of 15 January 2015, 184 patients with advanced NSCLC were in this group of patients who had progressed after at least 1 line of platinum-containing doublet chemotherapy for metastatic or locally advanced disease.

Of 184 patients, 22 had a confirmed objective response, including one CR and 21 PRs, resulting in a confirmed ORR of 12.0% (95% CI: 7.6, 17.5). The ORR based on confirmed and unconfirmed responses was 14.1% (95% CI: 9.4, 20.0), including 1 CR and 25 PRs. Based on confirmed or unconfirmed responses, 10 of 26 responding patients (39%) had responded by the first assessment at 6 weeks, and 19 of 26 (73%) had responded by 12 weeks. The median PFS was 11.6 weeks (95% CI: 8.4, 13.7), and Kaplan-Meier PFS rates at 24 weeks and 48 weeks were 26% (95% CI: 20, 33) and 18% (95% CI: 12, 26), respectively.

1.2.1.2. Clinical Experience in Patients with Locally Advanced or Metastatic UC

Study EMR 100070-001 evaluated avelumab in patients with locally advanced or metastatic UC who were either cisplatin ineligible or had progressive disease (PD) after at least 1 line of platinum-based therapy in 2 different cohorts. As of 19 March 2016, a combined 241 patients had been treated in the 2 UC cohorts, of whom 153 had at least 6 months of follow-up.

In the pooled group of 153 patients, the confirmed ORR by Independent Endpoint Review Committee (IERC) was 17.6% (95% CI: 10.9, 22.5) including 9 CRs and 18 PRs. Onset of response was documented by the first or second tumor assessment for 21 of the 27 confirmed responders (77.8%). The median PFS by IERC was 6.43 weeks (95% CI: 6.14, 11.43). The PFS rate at 24 weeks was 22.6% (95% CI: 16.0, 29.9).

1.2.1.3. Clinical Experience in Patients with Ovarian Cancer

Study EMR 100070-001 evaluated avelumab in patients with recurrent or refractory ovarian cancer who had progression within 6 months of platinum-based therapy or progression after subsequent therapy in previously relapsed patients. As of 23 October 2015, a total of 124 patients were enrolled with a median follow-up of 12.4 months (range, 2.5 to 23.2 months).

The ORR, based on confirmed and unconfirmed responses, was 9.7% (95% CI: 5.1, 16.3; 12 of 124 patients). In 6 of the 12 responders (50.0%), the responses were ongoing at the time of the data cutoff. In 6 patients, the onset of the response was at approximately 6 weeks. The onset of response for the other 6 responders occurred between Weeks 10 and 18. The median PFS was 11.3 weeks (95% CI: 6.1, 12.0 weeks). The Kaplan-Meier PFS rates were 16.1% (95% CI: 9.2, 24.7) and 5.5% (95% CI: 1.3, 14.2) at 24 and 48 weeks, respectively. Among the patients with baseline and at least on-treatment assessment of cancer antigen-125 (CA-125) (n=72), 13 patients (10.5%) showed a decrease in CA-125 anytime during treatment.

1.2.1.4. Clinical Experience in Patients with Advanced Breast Cancer

Study EMR 100070-001 evaluated avelumab in patients with metastatic breast cancer refractory to or progressing after standard-of-care therapy. As of 27 February 2015, 168 patients were enrolled; 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 TNBC, 26 patients (15.5%) were HER2-positive, and 12 patients (7.1%) had unknown biomarker status. At the time of the data cutoff, 9 patients (5.4%) remained on avelumab treatment. Unconfirmed ORR per Investigator assessment was 4.8% (95% CI: 2.1, 9.2), with 1 CR and 7 PRs across HER2/ER/progesterone receptor status. The median PFS was 5.86 weeks (95% CI: 5.86 to 6.00 weeks). The Kaplan-Meier PFS rates were 18.4% (95% CI: 12.9, 24.8), 10.1% (95% CI: 5.9, 15.5), and 5.6% (95% CI: 2.5, 10.7) at 12, 24, and 48 weeks, respectively.

1.2.1.5. Clinical Experience in Patients with mCRPC

Study EMR 100070-001 evaluated avelumab in patients with mCRPC. As of 31 December 2016, all 18 patients enrolled had permanently discontinued avelumab treatment. No patient had responses (confirmed or unconfirmed) and 10 patients (55.6%) achieved SD according to RECIST v.1.1 per investigator assessment. The median PFS was 5.4 months (95% CI: 1.4, 5.5 months). The Kaplan-Meier PFS rates at 3 and 6 months were 51.3% (95% CI: 24.0, 73.2) and 20.5% (95% CI: 3.5, 47.3) respectively.

1.2.1.6. Pharmacokinetics of Avelumab in Humans

Available pharmacokinetic 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 (PBMCs) during the entire dosing interval, as determined from *ex vivo* studies. Based on the *in vitro* TO data and the observed trough serum avelumab levels in the dose escalation cohorts of Study EMR100070-001, TO was predicted to reach or exceed 95% throughout the entire dosing interval in more subjects in the 10 mg/kg dose group than in the 3 mg/kg dose group.

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

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

Serious AEs (SAEs) occurred in 52 of 164 patients (31.7%) who received 1 mg QD talazoparib. SAEs occurring in ≥2% of patients were pleural effusion (4.3%), anemia and dyspnea (3.7% each), and neoplasm progression and thrombocytopenia (2.4% each). Fourteen patients had SAEs considered related to talazoparib, which included anemia (3.0%); thrombocytopenia (2.4%); platelet count decreased (1.2%); and increased transaminases, neutropenic sepsis, and vomiting (0.6% each).

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

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

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

In the ongoing Phase 3 study 673-301, 308 patients with locally advanced or metastatic breast cancer were treated as of the cutoff date. An estimated 206 patients were receiving talazoparib and 102 were receiving another single-agent chemotherapy of physician's choice, based on the 2:1 randomization scheme. A serious TEAE of veno-occlusive disease of the liver leading to death was assessed as related to talazoparib by the Investigator in a 34-year old female patient with advanced breast cancer metastatic to the axilla and bone who developed asymptomatic Grade 3 liver test abnormalities (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.

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 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. As of 13 February 2015, the proportion of patients with breast, ovarian/primary peritoneal, and pancreatic cancers with BRCA mutations who were treated with talazoparib at 1 mg QD and had objective responses according to RECIST v1.1 was 50% (7 of 14; 95% CI: 23.0, 77.0), 41.7% (5 of 12; 95% CI: 15.2, 72.3), and 20.0% (2 of 10), respectively. Cancer patients harboring BRCA mutations who are resistant to platinum-based chemotherapy display decreased sensitivity to PARP inhibitors.[20] Given the exploratory nature of Cohort F, pancreatic cancer patients in this cohort will not include patients who progressed within 6 months of starting previous platinum-based chemotherapy. This is aligned with the approach followed for other indications in this study. Responses were also reported in 2 patients with SCLC (8.7%; 2 of 23; 95% CI: 1.1, 28.0).

1.2.2.3. Clinical Efficacy in Patients with Germline BRCA 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 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 1 September 2016, the data cut-off for the primary analysis, 83 patients with locally advanced or metastatic breast cancer with deleterious germline BRCA 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.

In the ongoing Phase 3 EMBRACA study in patients with BRCA 1/2-positive locally advanced and/or metastatic breast cancer, single-agent talazoparib demonstrated superior PFS versus physician choice chemotherapy. Median PFS was 8.6 months (95% CI: 7.2, 9.3) for patients treated with talazoparib and 5.6 months (95% CI: 4.2, 6.7) for those treated with chemotherapy [hazard ratio: 0.54 (95% CI: 0.41, 0.71), $p<0.0001$].[1] Talazoparib was approved by the FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2- negative locally advanced or metastatic breast cancer.

1.2.2.4. 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 plasma concentration-time curve (AUC) while reduced the maximum plasma concentratioin (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 AST >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST) on talazoparib exposure. No dose adjustment is necessary for patients with mild hepatic impairment. 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 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 talazoparib starting dose for patients with moderate renal impairment is discussed in Section 1.2.6.2. The effect of renal impairment on talazoparib PK is also 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 with mCRPC Treated with PARP Inhibitors as a Single Agent or in Combination with Immunotherapy

The PARP inhibitor olaparib given as single agent was evaluated in a Phase 2 study in 50 patients with previously treated mCRPC.[25] 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). 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 was evaluated in a Phase 1/2 study in 10 patients with mCRPC. Overall, 8 out of 10 patients had a reduction in PSA level, including 5 patients who had declines in PSA level ≥50% from baseline. PSA level reductions were observed in patients with bone-only disease, in those who had bone disease and soft-tissue or visceral metastases, and in patients with or without mutations in DNA repair pathways.[26]

Veliparib given as a single agent was investigated in a Phase 1 dose-finding study in patients with advanced solid tumors; overall, 98 patients were enrolled, of whom 78 had disease with a germline BRCA defect.[27] Three patients with BRCA2 germline mutated mCRPC were enrolled at the recommended Phase 2 dose (RP2D) and were evaluable for response. In these patients, the ORR was 2/3 (66%) and all patients had a PSA reduction >50% with respect to baseline.

A Phase 1 study evaluated niraparib given as a single agent in 100 patients with advanced solid tumors.[28] A total of 23 mCRPC patients were enrolled and 21 of these received niraparib at 290 mg QD or 300 mg QD. No mCRPC patient achieved an objective response but 9 patients had an SD with a median duration of 254 days (range: 124–375 days) and 1 patient had a >50% decrease in the concentration of PSA and had remained on study for 306 days.

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.[29] 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.[30] 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.[31] 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.

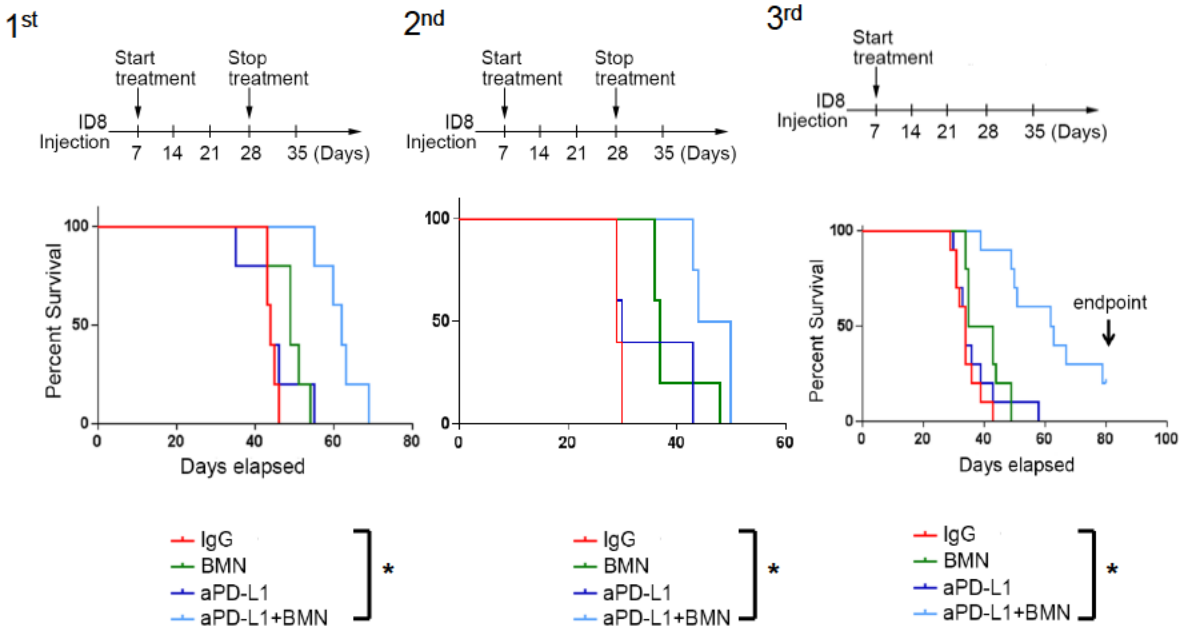
In keeping with these critical links between DNA damage and immune priming, talazoparib has been shown to drive the activation of STING and downstream target genes in cultured cell lines [redacted] and to promote T cell and NK cell infiltration and activation in a mouse model of ovarian cancer.[18]

[redacted]

[redacted]

However, talazoparib treatment has also been shown to lead to 2-3 fold increased expression of PD-L1 by tumor cells,[19] 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 (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.

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 ($p < 0.01$).

Given the proposed mechanism of the avelumab and talazoparib combination, one subgroup of patients likely to benefit from the combination will be those whose tumors are most sensitive to talazoparib. A number of biomarkers have the potential to identify patients with increased sensitivity to talazoparib,[21] and two of these biomarkers will be evaluated prospectively or retrospectively in the context of this study, as follows:

- Assessment of genomic scarring as measured via loss of heterozygosity (LOH).
- Presence of defects in a panel of DNA damage repair (DDR) genes.

Tumors with defects in DDR genes have also been shown to present with a more inflamed tumor phenotype in a number of settings,[22,23,24] and therefore, are also expected to respond better to avelumab treatment.

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 Sections 1.2.1.1, 1.2.1.2, 1.2.1.3, 1.2.2, 1.2.3, and 1.2.5), the avelumab and talazoparib combination is proposed for evaluation in patients with locally advanced or metastatic solid tumors.

1.2.5. Rationale for the Tumor Types to be Evaluated

Tumor types in the anti-PD-1/L1 naïve setting were selected based on one or more of the following, in settings of unmet medical need:

a. One of the investigational products, or an agent of the same class, has shown preliminary clinical activity in the tumor type of interest.

b. The tumor type has been reported, or is predicted, to have a high prevalence (≥30%) of defects in genes critical to DDR (eg, BRCA1/2, ATM, ataxia-telangiectasia and Rad3-related [ATR], the Fanconi anemia complementation [FANC] genes, and others). Defects in such genes have been reported to predict for sensitivity to PARP inhibitors,[21] such as talazoparib, and have also been shown to present with a more inflamed tumor phenotype, expected to lead to improved avelumab activity in a number of settings.[22,23,24] As such, tumors harboring these defects may respond more robustly to combination treatment with talazoparib and avelumab.

c. The tumor type has been reported, or is predicted, to have a high prevalence (≥35%) of genomic scarring, as defined by the homologous recombination deficiency (HRD) score.[32] Tumors with a high HRD score have been shown to have increased clinical benefit from PARP inhibitors,[33,34] As such, tumors with a high HRD might be expected to respond more robustly to the combination of talazoparib and avelumab.

NSCLC that has progressed on previous anti-PD-1/L1 treatment was selected as an area of high unmet medical need, in which the combination of avelumab and talazoparib could provide benefit. Re-challenge of patients, who have progressed during anti-PD-1/L1 therapy, with subsequent monotherapy anti-PD-1/L1 has met with only limited anecdotal success.[35] Resistance to anti-PD-1/L1 therapy is thought to occur via a number of potential mechanisms,[36] several of which rely on tumor cell extrinsic, immunosuppression of the antitumor immune response. Examples of such tumor cell extrinsic suppression mechanisms include increases in immunosuppressive cytokines and cell sub-sets (such as MDSCs and macrophages), reduced infiltration and activation of dendritic cells and a reduction in antigen presentation. Talazoparib is expected to reprogram the local immune microenvironment, overcoming these immunosuppressive pathways via the immune priming mechanisms outlined above, and as such the addition of talazoparib to anti-PD-L1, in anti-PD-1/L1 resistant patients, is hypothesized to overcome resistance and provide benefit to these patients.

PARP inhibition may have additional therapeutic benefit when combined with the anti-PD-L1 antibody avelumab. Talazoparib, via its ability to promote increased DNA damage, may promote key stages of tumor immune response following PD-L1 blockade. DNA damage has the potential to release tumor antigens into the tumor microenvironment that may promote an antitumor immune response and increase in the infiltration of tumor-specific immune cells.[37]

Additional solid tumors may be incorporated into this protocol via an amendment, based on emerging preclinical and clinical data.

1.2.6. Rationale for the Investigational Product Doses

1.2.6.1. 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 MCC. Avelumab was originally dosed on a mg/kg basis in order to reduce inter-subject variability in drug exposure. However, emerging data for mAbs, including the marketed PD-1 and PD-L1 immune checkpoint inhibitors nivolumab, pembrolizumab and atezolizumab, reveal that body weight-based dosing regimens do not result in less variability in measures of exposure over fixed (ie, body-weight independent) dosing regimens.[38,39,40] Additionally, fixed dosing offers the advantages of less potential for dispensing errors, shorter dose preparation times in a clinical setting, and greater ease of administration.

Population PK analysis was conducted based on the acquired data across 3 single-agent avelumab studies in 1827 patients with 14 different types of cancer. PK simulations suggest that exposures to avelumab across the available range of body weights are less variable with 800 mg Q2W compared with 10 mg/kg Q2W; exposures were similar near the population median weight. Low-weight subjects tended towards marginally lower exposures relative to the rest of the population when weight-based dosing was used, and marginally higher exposures when flat dosing was applied. However, the implications of these exposure differences are not expected to be clinically meaningful at any weight across the whole population. Furthermore, 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. Preliminary PK data for avelumab from patients enrolled in Phase 1b of this study confirm that in all 12 patients (weight range 55.9 kg to 105.1 kg) avelumab C_{trough} was considerably >1 μg/mL following 800 mg Q2W dose.

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. Flat dosing for avelumab of 800 mg Q2W has recently been approved in the US for the MCC and UC indications (avelumab United States Product Insert, 19 October 2018).

1.2.6.2. 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 that study at 1 mg/day demonstrated objective responses or clinical benefit (CR, PR, or SD ≥24 weeks) in patients with breast, ovarian/peritoneal, pancreatic cancer, SCLC, and Ewing sarcoma. The dose level of 1 mg QD is currently being used in the ongoing randomized Phase 3 study 673-301 in patients with locally advanced or metastatic breast cancer.

Based on preliminary population PK analysis from patients in Studies PRP-001 and PRP-002, the talazoparib CL/F was decreased by 44% from normal in patients with moderate renal impairment (CrCl 30-59 mL/min), and therefore in those patients the 1 mg QD talazoparib starting dose should be reduced to 0.75 mg QD, as discussed in the talazoparib IB.[12] In the Phase 1b portion of this study, only patients with a CrCl of ≥60 mL/min (as estimated using the Cockcroft-Gault formula) will be eligible for enrollment.

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. Nevertheless, 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. Preliminary PK data from the 12 patients in the Phase 1b cohort of this study support absence of a PK DDI between the 2 agents, with avelumab and talazoparib concentrations following co-administration similar to those observed when each is administered as monotherapy.

1.2.7. 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, mCRPC, UC and ovarian cancer in the expansion cohorts of the ongoing Phase 1 Study EMR 100070-001, as described in Sections 1.2.1.1, 1.2.1.2, 1.2.1.3, and 1.2.1.6. 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 AEs 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 and PTEN dysfunction, including breast cancer, ovarian/peritoneal cancer, and pancreatic cancer in the Phase 1 Study PRP-001, as described in Section 1.2.2.2. 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 SAEs mostly associated with myelosuppression. These AEs were primarily Grade 1 or 2 severity and typically resolved with temporary dose interruptions or reductions.

Based on 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.

The Phase 1b portion of this study has been completed, following evaluation of the first 12 enrolled patients. All patients had completed their first cycle with treatment of avelumab at 800 mg IV Q2W in combination with talazoparib 1 mg orally QD and were evaluable for DLT. 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 DLT rate of 0.25 was observed, with a total of 3 DLTs that warranted dose interruption and reduction (2 cases of Grade 3 thrombocytopenia and one case of Grade 3 neutropenia).

1.2.8. Rationale for Biomarker Assessments and Prospective Patient Selection

This study intends to characterize the activity of avelumab in combination with talazoparib, with the aim of increasing the clinical benefit seen historically with either single agent. The success of the combination will likely be contingent on identifying the specific tumor types and/or patients most likely to respond to the combination. A key mechanistic hypothesis underpinning the combination is that increased DNA damage and cell death mediated by talazoparib will lead to enhanced immune priming and tumor immunogenicity, enabling a more effective anti-tumor immune response to be promoted by avelumab. Given this hypothesis, one subgroup of patients likely to benefit from the combination will be those whose tumors are most sensitive to talazoparib-mediated cell death and DNA damage. A number of biomarkers have the potential to identify patients with such increased sensitivity to talazoparib,[21] and two of these will be employed in the context of this study (ie, assessment of genomic scarring, as measured by LOH, and presence of defects in a panel of DDR genes). In cohorts for NSCLC (Cohort A1), TNBC (Cohort B1), ovarian cancer (Cohort C1), and UC (Cohort D), these 2 biomarkers are expected to occur at a prevalence sufficient to allow for meaningful retrospective analysis of an unselected group of patients, given the selected sample sizes. In cohorts for NSCLC (Cohort A2), HR+/HER2- breast cancer (Cohort B2) and mCRPC (Cohort E2), the prevalence of both biomarkers, or cohort size, is low enough that a prospective selection is considered necessary in order to enable recruitment of a sufficient number of patients to support meaningful analysis. With respect to prospective patient selection, patients will be considered DDR+, and eligible for entry into cohorts A2, B2 and E2, if they have a previously documented defect in a predefined panel of DDR genes, or if they test positive for defects in a predefined panel of DDR genes or if they have a LOH score above a cutoff defined by the assay specifications.

In addition to the 2 biomarkers described above, defects in BRCA1, BRCA2, and ATM have been extensively explored and validated as biomarkers of sensitivity to PARP inhibition,[3] particularly in ovarian cancer.[41] Given this context, 2 additional cohorts will prospectively select patients who test positive for defects in these genes. The first, Cohort C2, will prospectively select for ovarian cancer patients with germline or somatic defects in BRCA1 or BRCA2. The second, Cohort F, will prospectively select for patients with locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic, germline or somatic defects in BRCA1, BRCA2, or ATM genes.

Complementing the DDR biomarkers described above, a number of assessments will be undertaken 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. These assessments may include, but are not limited to, assessment of PD-L1 expression by tumor and/or immune cell types in the tumor using immunohistochemistry, 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 collection of pre-treatment tumor specimens, including 1) a tumor tissue sample from a biopsy performed during, or within 1 year (5 years for mCRPC patients with no biopsable lesion outside of bone at screening) of, the screening period and 2) an archival tissue sample where available, is mandatory.

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 pre-treatment and post-treatment. The primary aim of these measurements is to identify pharmacodynamic or mechanistic biomarkers for the combination of avelumab and talazoparib. Such biomarkers may help to inform the optimal dose and schedule, and when taken at baseline, may also have value in predicting response to treatment. Planned assessments include, but are not limited to, gene expression profiling, diversity of TCR sequences by DNA sequencing, and levels of circulating soluble factors such as cytokines and chemokines.

In the event that clinical benefit is not observed or is transient, assessment of reasons for lack of benefit may help guide patient selection for future development of the combination. For these reasons, tumor biopsies performed at the End-of-Treatment (EOT) 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 EOT tumor biopsies may be discontinued.

1.2.9. 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

2.1. Objectives

Primary Objectives

- Phase 1b: To assess the DLT rate of avelumab in combination with talazoparib in patients with locally advanced or metastatic solid tumors in order to select the RP2D of talazoparib for the combination.

- Phase 2: To assess ORR of avelumab in combination with talazoparib, as assessed by the Investigator, per RECIST v1.1 in patients with locally advanced or metastatic solid tumors and per RECIST v1.1 and Prostate Cancer Working Group 3 (PCWG3) in patients with mCRPC.

Secondary Objectives

- 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 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, tumor mutational burden (TMB; defined as the total number of mutations in the tumor genome, or number of mutations per megabase of DNA if derived from targeted sequencing),[4] and potential biomarkers of PARP inhibitor sensitivity in baseline tumor tissue.

[redacted]

2.2. Endpoints

Primary Endpoint

- Phase 1b: DLT during the DLT evaluation period (Cycle 1).
- Phase 2: Confirmed OR, as assessed by the Investigator using RECIST v1.1 in patients with locally advanced or metastatic solid tumors (see Appendix 3) and RECIST v1.1 and PCWG3 in patients with mCRPC (see Appendix 5).

Secondary Endpoints

- AEs as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for AEs [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 for avelumab and talazoparib including: pre-dose/trough concentrations (C_{trough}) and post-dose concentrations (for talazoparib) or maximum concentrations (C_{max}) for avelumab.
- Avelumab anti-drug antibody (ADA) levels and neutralizing antibodies (Nab) against avelumab.
- Phase 1b: Confirmed OR, as assessed by the Investigator using RECIST v1.1 in patients with locally advanced or metastatic solid tumors and RECIST v1.1 and PCWG3 in patients with mCRPC.

- Phase 1b and Phase 2: Time-to-event endpoints including time to tumor response (TTR), duration of response (DR), and PFS as assessed by the Investigator using RECIST v1.1 for patients with solid tumors and using RECIST v1.1 and PCWG3 for patients with mCRPC, time to PSA progression for patients with mCRPC, and OS.
- PSA response ≥50% for patients with mCRPC.
- CA-125 response for patients with ovarian cancer.
- PD-L1 expression level in baseline tumor tissue.
- TMB in baseline tumor tissue.
- Genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue.

[redacted]

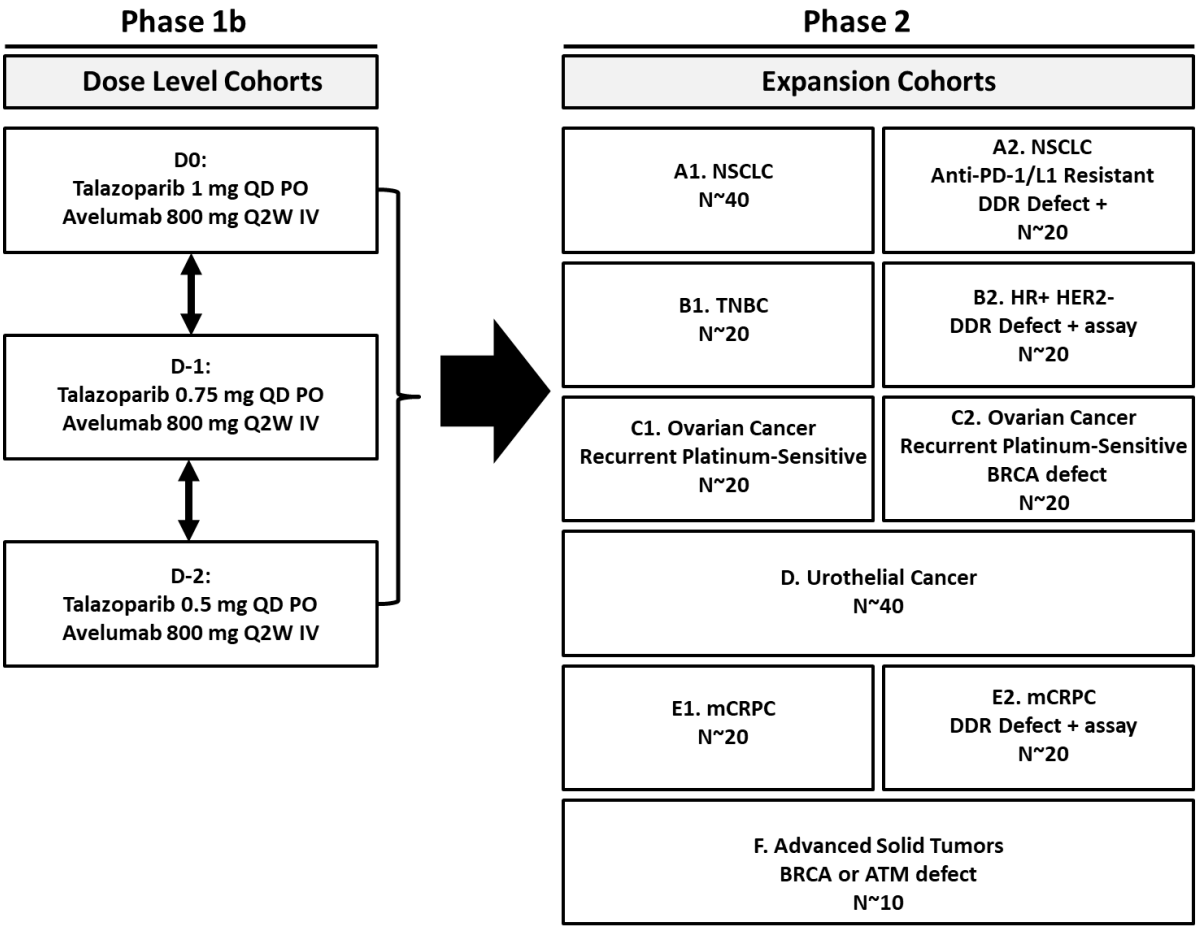
3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1b/2, open label, multi-center, study of avelumab in combination with talazoparib in adult patients with locally advanced (primary or recurrent) or metastatic solid tumors including NSCLC, TNBC, HR+/HER2- breast cancer, recurrent platinum-sensitive ovarian cancer, UC, mCRPC, and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic or likely pathogenic germline or somatic defects in BRCA1, BRCA2, or ATM genes. Approximately 242 patients in total will be enrolled into the study. A given cohort size may be expanded by a limited number of additional patients (approximately 10) per Sponsor's discretion subsequent to the identification of any early signal of clinical activity that may emerge from the generated data in a biomarker-defined population.

The study design and tumor-specific expansion cohorts, including the number of patients to be enrolled into each cohort, are shown in Figure 3.

Figure 3. Phase 1b and Phase 2 Study Design Schema



ATM= ataxia telangiectasia mutated; BC= breast cancer; BRCA=BReast CAncer susceptibility gene; mCRPC= metastatic castration-resistant prostate cancer; D=Dose; HER2-=human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; DDR=DNA damage repair; DDR Defect +=DDR defect positive, as determined by the Foundation One assay or validated local assay result; IV=intravenous; NSCLC=non-small cell lung cancer; PD-L1= Programmed Death-Ligand 1; PO=orally; Q2W=every 2 weeks; QD=every day; TNBC= triple-negative breast cancer; TPS= tumor proportion score.

3.1.1. Phase 1b

During the Phase 1b portion of this study, patients with locally advanced or metastatic solid tumors, who meet eligibility criteria, will be treated with one of up to 3 different doses of talazoparib (0.5 mg, 0.75 mg or 1.0 mg) administered orally QD in combination with a fixed dose of avelumab 800 mg IV Q2W, and will be evaluated for DLTs. The modified toxicity probability interval (mTPI) method will be used to identify the RP2D for talazoparib (see Appendix 4). The avelumab and talazoparib combination will be administered in 28-day cycles. The DLT evaluation period will be 28 days (ie, Cycle 1). The target enrollment cohort size is 3-6 patients.

The starting dose level will be 1.0 mg talazoparib QD plus 800 mg avelumab Q2W. For patients with moderate renal impairment (CrCl 30-59 mL/min), the 1 mg QD talazoparib starting dose should be reduced to 0.75 mg QD (Section 1.2.6.2). The dose levels of the combination to be evaluated are included in Table 3.

Table 3. Talazoparib and Avelumab Dose Levels

Dose Level	Talazoparib Dose (Oral)	Avelumab Dose (IV)
D0	1 mg QD	800 mg Q2W
D-1	0.75 mg QD	800 mg Q2W
D-2	0.5 mg QD	800 mg Q2W

D=dose; QD=once daily; Q2W=every 2 weeks

In Phase 1b, patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of the investigational products in Cycle 1 for reasons other than treatment-related toxicity are not evaluable for DLT. Additional patients will be enrolled in the specific enrollment cohort to replace patients who are not considered DLT-evaluable.

The Phase 1b portion is completed when at least 12 DLT-evaluable patients have been treated at the highest dose associated with DLT rate <0.33 (see Section 9.2). Early completion of the Phase 1b portion can be reached when 9 or more DLT-evaluable patients have been treated at the same dose level with no occurrence of DLT, as the DLT rate of <0.33 will be met.

Once the Phase 1b portion is completed and the RP2D of the combination is determined, the Phase 2 portion will be initiated.

Approximately 12-36 patients are expected to be enrolled in Phase 1b using the mTPI method.

If dose level D-2 is not tolerable, the study will be stopped and no dose combination will be further evaluated.

Phase 1b was completed in May 2018 with 12 patients enrolled.

In May 2018, the RP2D for talazoparib administered orally in combination with avelumab 800 mg IV Q2W was confirmed to be 1 mg QD. The talazoparib starting dose for patients with moderate renal impairment (CrCl 30-59 mL/min) will be reduced to 0.75 mg/day as discussed in the talazoparib IB.[12]

3.1.1.1. Rules for Dose De-Escalation/Escalation in Phase 1b

Starting with dose level D0, 3 patients will be enrolled, treated, and monitored during the 28-day DLT evaluation period.

The dose escalation/de-escalation rules for talazoparib administered in combination with avelumab will follow the mTPI method (overview provided here and described in greater detail in Section 9.2). The mTPI method recommends the dose level for the next enrollment cohort of patients based on the number of DLT-evaluable patients treated at the current dose level that have reported DLTs. Briefly, the mTPI method relies upon a statistical probability algorithm, calculated using all patients treated in prior and current enrollment cohorts at the same dose level to determine where future enrollment cohorts should involve dose re-escalation, no change in dose, or dose de-escalation. The detailed dose escalation/de-escalation rules based on the mTPI method are illustrated in Appendix 4.

When all DLT-evaluable patients treated in a given enrollment cohort have completed the DLT observation period (28 days; Cycle 1) or experienced a DLT, whichever occurs first, the patients in the next cohort will receive the dose level of the combination as assigned by the mTPI design. As an example, if the total number of DLT-evaluable patients (cumulative in the Phase 1b from prior and current cohorts) treated at the current dose combination is 3, the dose escalation/de-escalation rules are described below:

- 0 DLT in 3 DLT-evaluable patients → escalate, if a higher dose level is available;
- 1 DLT in 3 DLT-evaluable patients → remain at the same dose level;
- 2 DLTs in 3 DLT-evaluable patients → de-escalate, if a lower dose level is available and allow for possible re-escalation;
- 3 DLTs in 3 DLT-evaluable patients → de-escalate, if a lower dose level is available and consider current dose as intolerable.

3.1.2. Phase 2

The overall available data (including safety and preliminary anti-tumor activity) emerging from the Phase 1b portion of the study will be evaluated before starting enrollment of patients in the Phase 2 portion of the study. The Phase 2 portion of this study will further assess the safety and preliminary anti-tumor activity of the avelumab and talazoparib combination at the RP2D. Phase 2 expansion cohorts will include patients with locally advanced (primary or recurrent) or metastatic NSCLC, TNBC, HR+/HER2- breast cancer, recurrent platinum-sensitive ovarian cancer, UC, mCRPC, and locally advanced (primary or recurrent) or metastatic solid tumors harboring pathogenic, or likely pathogenic, germline or somatic defects in BRCA1, BRCA2, or ATM genes.

As of May 2018, the RP2D for talazoparib administered orally in combination with avelumab 800 mg IV Q2W was confirmed to be 1 mg orally QD. The safety profile of the combination at the tested dose level is generally consistent with the safety profiles from the individual components and is generally manageable.

Approximately 230 patients are expected to be enrolled in Phase 2.

A given cohort size may be expanded by a limited number of additional patients (approximately 10) per Sponsor's discretion subsequent to the identification of any early signal of clinical activity that may emerge from the generated data in a biomarker-defined population.

3.2. Dose-Limiting Toxicity Definition

Severity of AEs will be graded according to NCI CTCAE v4.03. In the Phase 1b portion of the study, any of the following AEs occurring during the DLT observation period (Cycle 1; a cycle will be 28 days in duration), which are attributable to one or both of the investigational products will be classified as DLTs:

Hematologic:

- Grade 4 neutropenia (absolute neutrophil count [ANC] $<500/mm^3$ or $<0.5 \times 10^9/L$) lasting >5 days;
- Febrile neutropenia, defined as ANC $<1000/mm^3$ with a single temperature of >38.3°C (>101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour;
- Neutropenic infection (ANC $<1,000/mm^3$ or $<1.0 \times 10^9/L$, and Grade >3 infection);
- Grade ≥3 thrombocytopenia (platelet count $<50,000$ mm^3 or $<50.0 \times 10^9/L$) with bleeding;
- Grade 4 thrombocytopenia (platelet count $<25,000/mm^3$ or $<25.0 \times 10^9/L$);
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated).

Non-Hematologic:

- Grade ≥3 toxicities of any duration except:
  - Grade 3 nausea, vomiting, or diarrhea and Grade 4 vomiting or diarrhea in the absence of maximal medical therapy that resolves in 72 hours;
  - Grade 3 fatigue lasting <5 days;
  - Grade 3 hypertension that can be controlled with medical therapy;
  - An increase of indirect (unconjugated) bilirubin indicative of Meulengracht/Gilbert's syndrome;
  - Grade 3 serum lipase and/or serum amylase ≤7 consecutive days without clinical signs or symptoms of pancreatitis;

  - Grade ≥3 laboratory abnormalities without a clinical correlate and that do not require medical intervention;
  - Grade ≥3 laboratory abnormalities that do not represent a clinically relevant shift from baseline;
  - Grade 3 endocrinopathies controlled with hormonal therapy.
- Potential Hy's Law cases defined as: ALT or AST >3 × ULN if normal at baseline OR >3 × ULN and doubling the baseline (if >ULN at baseline) associated with total bilirubin >2 × ULN and an alkaline phosphatase <2 × ULN.

Non-Adherence to Treatment Schedule:

- Failure to deliver at least 75% of the planned doses of talazoparib during the first cycle of treatment due to treatment-related toxicities;
- Grade 3 non-hematologic toxicity that delays administration of either study drug for more than 2 weeks.

Dose Reductions:

- Any AE that results in a dose reduction of talazoparib, as per Section 5.4.6.2 and 5.4.6.3.

While the rules for adjudicating DLTs in the context of the Phase 1b portion of the study are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT observation period may be defined as a DLT after consultation between the Sponsor and Investigator, based on the emerging safety profile for the combination.

3.3. Maximum Tolerated Dose Definition

The MTD estimate is the highest dose level of the combination that is associated with a DLT rate <0.33 among the DLT-evaluable patients treated at that dose level.

3.4. Maximum Administered Dose Definition

The maximum administered dose (MAD) is the highest dose level of the combination administered. In this clinical study, the MAD is also the starting dose of the combination in Phase 1b, which is talazoparib 1 mg QD in combination with avelumab 800 mg IV Q2W.

3.5. Recommended Phase 2 Dose (RP2D) Definition

The RP2D is the dose level of the combination that will be chosen for further clinical development and for evaluation in the Phase 2 portion of the study.

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.

4.1. Inclusion Criteria

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

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

    a. NSCLC: Phase 1b and Phase 2 Cohort A1

    - Have received 0-2 prior- chemotherapy regimens for locally advanced or metastatic NSCLC. If previously treated with platinum-based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum-based chemotherapy is allowed.

      Applicable to South Korean Investigator Sites Only: have received 1 but no more than 2 prior chemotherapy regimens for locally advanced or metastatic NSCLC, unless the patient is not a candidate for such therapy or does not tolerate such therapy. If previously treated with platinum based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum based chemotherapy is allowed.

    - 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 with known B-Raf proto-oncogene $(BRAF)^{V600}$ mutations or ALK and c-Ros oncogene 1 (ROS1) translocations/rearrangements must have received the appropriate targeted therapy if available. Patients with activating EGFR mutations are not eligible; non-squamous cell histologies require testing if EGFR status is unknown.

    Phase 2 Cohort A2

    - Have received 1 prior systemic treatment regimens for locally advanced or metastatic NSCLC. This includes 1 but no more than 1 prior regimen of anti-PD-1/L1 therapy in the metastatic (Stage IV) setting, either as single agent or in combination with a platinum containing chemotherapy regimen, as their most recent treatment regimen. Patients must not have progressed for at least 6 months since the start of this regimen.

- Patients with known $BRAF^{V600}$ mutations or ALK and ROS1 translocations/rearrangements must have received the appropriate targeted therapy if available. Patients with activating EGFR mutations are not eligible; non-squamous cell histologies require testing if EGFR status is unknown.

- Disease is DDR defect positive, as determined by the presence of a previously documented -known or likely deleterious/pathogenic defect in one of the following 34 DDR genes: ATM; ATR; BRCA1; BRCA2; BRIP1; CDK12; CHEK1; CHEK2; ERCC4; FANCA; FANCC; FANCG; FANCL; MLH1; MRE11A; MSH2; MSH6; MUTYH; NBN; PALB2; PARP1; PARP2; PARP3; PMS2; POLD1; POLE; RAD51; RAD51B; RAD51C; RAD51D; RAD52; RAD54L; XRCC2; XRCC3.

  Presence of such a defect must have been established via a tissue based next generation sequencing test, performed --in a CAP/CLIA-certified (or comparable local or regional certification) laboratory, or via a germline test from one of the following approved providers: Myriad Genetics; Invitae; Ambry; Quest; Color Genomics; MSKCC-IMPACT; GeneDx; Foundation Medicine.

  Where the presence of a qualifying defect in one of the listed genes has not been determined, the mandatory DDR Defect sample must be sent to the Foundation Medicine central laboratory, no more than 45 days prior to enrollment, for prospective testing to confirm eligibility. See Schedule of Activities for tissue requirements for the Foundation One test.

b. Breast Cancer:

   Phase 1b: Triple-Negative Breast Cancer (TNBC) defined as ER- and PgR-negative (immunohistochemistry [IHC] nuclear staining <1%) and HER-2 negative (IHC 0, 1+ or 2+ and/or ISH non-amplified with ratio less than 2.0).

   - Have received at least 1 prior chemotherapy regimen for locally advanced or metastatic breast cancer. If previously treated with a platinum-based chemotherapy in the advanced/metastatic setting, the patient must not have progressed while on treatment with the most recent platinum-based chemotherapy.

   - Previous neoadjuvant/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. If previously treated with neoadjuvant/adjuvant platinum-based chemotherapy, the patient must not have progressed while on treatment or within 6 months after stopping the platinum-based chemotherapy.

- There is no limit on the number of prior hormonal 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 (VEGF).

Phase 2 (Cohort B1): -TNBC:

- Have received 0-2 prior chemotherapy regimens for locally advanced or metastatic breast cancer. If previously treated with a platinum-based chemotherapy in the advanced/metastatic setting, the patient must not have progressed while on treatment with the most recent platinum-based chemotherapy.

  Applicable to South Korean Investigator Sites Only: have received 1 but no more than 2 prior chemotherapy regimens for locally advanced or metastatic TNBC, unless the patient is not a candidate for such therapy or does not tolerate such therapy. If previously treated with platinum based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum based chemotherapy is allowed.

- Previous neoadjuvant/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. If previously treated with neoadjuvant/adjuvant platinum-based chemotherapy, the patient must not have progressed while on treatment or within 6 months after the last dose of platinum-based chemotherapy.

- There is no limit on the number of prior hormonal 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 (VEGF).

Phase 2 only (Cohort B2): --HR+/HER2- Breast Cancer:

- Cohort B2 only: Disease is DDR defect-positive, as determined by the presence of a previously documented known or likely deleterious/pathogenic defect in one of the following 34 DDR genes: ATM; ATR; BRCA1; BRCA2; BRIP1; CDK12; CHEK1; CHEK2; ERCC4; FANCA; FANCC; FANCG; FANCL; MLH1; MRE11A; MSH2; MSH6; MUTYH; NBN; PALB2; PARP1; PARP2; PARP3; PMS2; POLD1; POLE; RAD51; RAD51B; RAD51C; RAD51D; RAD52; RAD54L; XRCC2; XRCC3.

- Presence of such a defect must have been established via a tissue based next generation sequencing test, performed in a CAP/CLIA-certified (or comparable local or regional certification) laboratory, or via a germline test from one of the following approved providers: Myriad Genetics; Invitae; Ambry; Quest; Color Genomics; MSKCC-IMPACT; GeneDx; Foundation Medicine.

- Where the presence of a qualifying defect in one of the listed genes has not -been determined, the mandatory DDR Defect sample must be sent to the Foundation Medicine central laboratory, no more than 45 days prior to enrollment, for prospective testing to confirm eligibility. See Schedule of Activities for tissue requirements for the Foundation One test.

- Have received 0-2 prior chemotherapy regimens for locally advanced or metastatic breast cancer following standard hormone therapy. If previously treated with a platinum-based chemotherapy in the advanced setting, the patient must not have progressed while on treatment with the most recent platinum-based chemotherapy.

- There is no limit on prior hormonal therapies or targeted anti-cancer therapies such as mTOR or CDK4/6 inhibitors, or VEGF.

- Previous neoadjuvant/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. If previously treated with neoadjuvant/adjuvant platinum-based chemotherapy, the patient must not have progressed while on treatment or within 6 months after the last dose of platinum-based chemotherapy.

a. Recurrent Epithelial Ovarian Cancer:

   Phase 1b:

   - Have been previously treated with at least 1 prior platinum-based chemotherapy regimen.

   - No disease progression while on treatment; disease progression within 6 months after stopping the last platinum-based chemotherapy is required, also termed “platinum resistant recurrent disease”.

   Phase 2: Cohorts C1 and C2:

   - Have been previously treated with 1-2 prior platinum-based chemotherapy regimens for locally advanced or metastatic ovarian cancer and received platinum-based chemotherapy as their last treatment.

- No disease progression while on treatment or within 6 months after stopping the last platinum-based chemotherapy, also termed "platinum sensitive recurrent disease".

- *Cohort C2 only:* Patients must have a germline or somatic BRCA1 or BRCA2 gene defect based on a previous test result. The result must have been obtained from one of the following test providers: Myriad Genetics, Invitae, Ambry, Quest, Color Genomics, MSKCC-IMPACT (germline), Foundation Medicine (tissue or ctDNA based), Guardant, or other Clinical Laboratory Improvement Amendments (CLIA) approved tissue based next generation sequencing-based assay.

b. Transitional Cell Carcinoma of the Urothelium (UC) including Bladder, Urethra, Ureters, or Renal Pelvis:

   Phase 1b:

   - Have received at least 1 prior systemic platinum-based chemotherapy regimen for locally advanced or metastatic UC unless deemed ineligible for platinum-based chemotherapy. If disease progression occurred while on treatment or within 12 months after the last treatment dose, neoadjuvant/adjuvant chemotherapy or chemotherapy as part of a chemotherapy-radiotherapy regimen is counted as 1 prior treatment regimen towards the allowed limit of prior treatment regimens.

   - If previously treated with platinum-based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum-based chemotherapy is required.

   Phase 2: Cohort D:

   - Have received 0-2 prior systemic platinum-based chemotherapy regimens for locally advanced or metastatic UC. If disease progression occurred while on treatment or within 12 months after the last treatment dose, neoadjuvant/adjuvant chemotherapy or chemotherapy as part of a chemotherapy-radiotherapy regimen is counted as 1 prior treatment regimen towards the allowed limit of prior treatment regimens.

     Applicable to South Korean Investigator Sites Only: have received 1 but no more than 2 prior chemotherapy regimens for locally advanced or metastatic UC, unless the patient is not a candidate for such therapy or does not tolerate such therapy. If previously treated with platinum-based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum based chemotherapy is allowed.

- If previously treated with platinum-based chemotherapy, the patient must not have progressed while on treatment; disease progression after discontinuation of the platinum-based chemotherapy is allowed.

c. Metastatic CRPC without small cell features (Phase 1b, Phase 2: Cohorts E1 and E2):

- 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.

- Have received at least 1 but no more than 2 prior chemotherapy regimens for mCRPC, or were deemed unsuitable, declined, or did not have access to these therapies. Patients may have received radium-223, which does not count for a line of prior chemotherapy regimen.

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

- 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.

  - Soft tissue disease progression as defined by RECIST v1.1.

  - Bone disease progression defined by PCWG3 (see Appendix 5) with 2 or more new metastatic lesions on bone scan (confirm ambiguous results by other imaging modalities).

- Cohort E2 only: Disease is DDR defect-- positive, as determined by the presence of a previously documented known or likely deleterious/pathogenic defect in one of the following 34 DDR genes: ATM; ATR; BRCA1; BRCA2; BRIP1; CDK12; CHEK1; CHEK2; ERCC4; FANCA; FANCC; FANCG; FANCL; MLH1; MRE11A; MSH2; MSH6; MUTYH; NBN; PALB2; PARP1; PARP2; PARP3; PMS2; POLD1; POLE; RAD51; RAD51B; RAD51C; RAD51D; RAD52; RAD54L; XRCC2; XRCC3.

Presence of such a defect must have been established via a tissue based next generation sequencing test, performed in a CAP/CLIA-certified (or comparable local or regional certification) laboratory, or via a germline test from one of the following approved providers: Myriad Genetics; Invitae; Ambry; Quest; Color Genomics; MSKCC-IMPACT; GeneDx; Foundation Medicine.

Where the presence of a qualifying defect in one of the listed genes has not been determined, the mandatory DDR Defect sample must be sent to the Foundation Medicine central laboratory, no more than 45 days prior to enrollment, for prospective testing to confirm eligibility. See Schedule of Activities for tissue requirements for the Foundation One test.

d. Advanced solid tumor with a germline or somatic BRCA1, BRCA2 or ATM gene defect (Phase 2 Cohort F) not eligible for Phase 2 Cohorts A1, A2, B1, B2, C1, C2, D, E1, or E2:

- Patients must have a germline or somatic BRCA1, BRCA2 or ATM gene defect based on a previous test result. The result must have been obtained from one of the following test providers: Myriad Genetics, Invitae, Ambry, Quest, Color Genomics, MSKCC-IMPACT (germline), Foundation Medicine (tissue or ctDNA based), Guardant, or other CLIA approved tissue based next generation sequencing-based assay.

- Recurrent Epithelial Ovarian Cancer:

  - Patients must have received at least 1 but no more than 6 total prior cytotoxic chemotherapy regimens, including at least 1 course of platinum-based therapy. Maintenance therapies begun with cytotoxic chemotherapy and continued following best response will count as a single line of therapy.

  - Patients must not have progressed during or within 1 month after stopping the most recent platinum-based chemotherapy.

  - Platinum sensitivity requirements:

    - If previously treated with ≤2 prior cytotoxic chemotherapy regimens, patients must have progressed within 6 months after stopping the platinum-based chemotherapy, also termed “platinum resistant recurrent disease”.

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

- Metastatic pancreatic ductal adenocarcinoma (mPDAC):
  - 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 [oxaliplatin, irinotecan, fluorouracil, and leucovorin] or a gemcitabine-containing regimen) OR were deemed unsuitable, or declined these therapies.
  - If previously treated with FOLFIRINOX or other platinum-containing chemotherapy, the patient must not have progressed within 6 months of initiation of oxaliplatin treatment.
- Any other advanced solid tumor:
  - Have received at least one prior standard of care regimen, if it exists, as appropriate for the respective tumor type unless deemed intolerable, unsuitable, or declined these therapies.
  - If previously treated with neoadjuvant/adjuvant platinum-based chemotherapy, the patient must not have progressed while on treatment or within 6 months after stopping the platinum-based chemotherapy.
  - If previously treated with platinum-based chemotherapy in the advanced/metastatic setting, the patient must not have progressed within 6 months of initiation of platinum-based chemotherapy.

2. Measurable disease by RECIST v1.1 with at least 1 measurable lesion; This criterion is not required for patients with mCRPC.

3. Mandatory primary or metastatic tumor biopsy to be performed within 28 days (45 days for patients requiring prospective biomarker testing for eligibility evaluation) prior to study enrollment to allow FFPE tissue be submitted for protocol-required testing. Core needle or excision biopsies are required, as fine needle aspirations will not yield enough tissue for protocol-specified testing. If archival tumor tissue is available from a biopsy/surgery that was performed within 1 year prior to study enrollment and the patient did not receive any subsequent systemic anti-cancer treatment, the tumor tissue may be submitted without repeating a tumor biopsy during the screening period. For mCRPC patients with no biopsable lesion outside of bone, archival tumor tissue from a biopsy/surgery performed within 5 years prior to study enrollment must be submitted without repeating a tumor biopsy during the screening period.

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

5. ECOG Performance Status 0 or 1.

6. 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 × 10^9/L;

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

c. Hemoglobin ≥9 g/dL (≥5.6 mmol/L).

7. Adequate renal function, defined by an estimated CrCl of ≥60 mL/min for patients enrolled in Phase 1b portion of the study and ≥30 mL/min for patients enrolled in Phase 2 portion of the study. CrCl should be estimated according to the Cockcroft-Gault formula as:

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

NOTE: Patients enrolled in Phase 2 portion of the study with moderate renal impairment (30-59 mL/min) will receive a reduced starting dose for talazoparib of 0.75 mg QD.

8. Adequate Liver Function, including:

   a. Total serum bilirubin ≤1.5 × ULN;

   b. AST and ALT ≤2.5 × ULN.

9. Female patients of childbearing potential must have negative serum pregnancy or urine pregnancy test at screening (see Section 7.1.1 for criteria to be considered not of childbearing potential).

   Female patients of nonchchildbearing potential must meet at least 1 of the following criteria:

   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   - Have medically confirmed ovarian failure.

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

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

11. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other 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 IL-2, IFN--α, or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, OX-40, GITR, LAG-3, IDO, TDO, TIM-3, CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways. Prior treatment with Sipuleucel-T for patients with mCRPC is allowed.
   EXCEPTION for Cohort A2 only: Prior treatment with anti-PD-1/L1 therapy in the **metastatic** setting (**Stage IV only**) as described in Inclusion Criterion 1 is allowed.

3. Prior anti-cancer therapy within 2 weeks prior to study enrollment. Prior radiation therapy within 2 weeks prior to enrollment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided it has been completed 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 (see Section 5.7.5).

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

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

   c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

6. Known prior severe hypersensitivity to investigational products or any component in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies (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. Vaccination within 4 weeks of study enrollment and while on trials is prohibited except for administration of inactivated vaccines.

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 enrollment 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.

18. Clinically significant (ie, active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrollment), myocardial infarction (<6 months prior to 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 within 7 days prior to first dose of study drug, or anticipated use during the study of a strong P-gp inhibitor (See Section 5.7.10 for specific list of medications).

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 5 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 of the cervix. For patients not enrolled in Cohorts E1 and E2: low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation, or castration) or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms is allowed.

24. Pregnant female patients; breastfeeding female patients; female patients of childbearing potential who are unwilling or unable to use 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 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 a 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 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.

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 woman of child-bearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

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 investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational 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 IV in combination with talazoparib 0.5 mg, 0.75 mg, or 1.0 mg orally QD.

Assignment of patient number, patient enrollment, and allocation of study treatment by dose level (Phase 1b) and cohorts at the RP2D (Phase 2) 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, including the date, time, and dose of study drug will be recorded. The Investigator will make sure that the information entered into the case report form (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 investigational site by well-trained medical staff. The start and stop times of the avelumab infusion, along with the total volume administered, will be recorded in the patients' medical records. Additionally, the start and stop times of any interruptions to infusions and/or changes in rate of avelumab infusion will also need to be recorded in the patients' medical records. The vials of avelumab that are assigned and prepared for patients will be recorded in the pharmacy records. These records will all be available for Sponsor representatives to verify compliance.

The site will complete the required dosage Preparation Record located in the Investigational Product manual (IP manual) for avelumab. The use of the 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 and administration of the avelumab dose, including date of infusion, total dose administered, start and stop times of the infusion, and any reasons that a dose other than the protocol-specified dose or dosing schedule was administered. 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 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, then the patient would also be considered noncompliant.

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 will 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.

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 diary and dosing records that are included in the medical chart.

Patients will be considered out of compliance if ≥20% of the expected doses of each treatment are missed within a given cycle.

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 Practice 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 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.

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.[44] 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 investigative site, the following must occur in the order specified:

1. All required tests and assessments will be performed, as per the Schedule of Activities 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 will be taken QD at 0.5 mg, 0.75 mg, or 1 mg starting on Cycle 1 Day 1 (C1D1) and treatment should continue until EOT. 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.

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, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30-60 minutes prior to the first 4 infusions of avelumab (ie, Cycles 1-2) is mandatory (eg, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses (ie, ≥ Cycle 3) based on clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate. Prophylactic corticosteroids are not permitted.

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 investigational site on an outpatient basis on Day 1 and Day 15 of each 28-day cycle. Investigational 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 2 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. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. If a hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. In order to mitigate avelumab infusion-related reactions, patients have to be premedicated, according to guidance in Section 5.4.3.

Following the infusions of avelumab, patients must be observed for at least 30 minutes post-infusion for potential infusion-related reactions.

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 AEs 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.

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 in Table 4.

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 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 Grade ≤1 (hemoglobin ≥10 g/dL) or 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 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	• Hold avelumab. • Re-initiate avelumab once toxicity Grade ≤1 or baseline. • Permanently discontinue avelumab if toxicity does not

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

	Talazoparib	Avelumab
	• >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.	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).
Non-hematologic Toxicities		
Grade 1 and Grade 2	• No requirement for dose interruption or dose reduction. • For suspected immune-related toxicities due to avelumab that require avelumab delay or discontinuation as per Section 5.4.6.5, 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.
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	• 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
	4 weeks. • **Exceptions are:** Laboratory values that do not have any clinical correlate. • Permanenlty 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.	
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 subject. • Subjects 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 v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 • **Diarrhea:** <4 stools/day over Baseline; • **Colitis:** asymptomatic .	• Continue avelumab therapy; • Symptomatic treatment (eg, loperamide).	• Close monitoring for worsening symptoms; • Educate subject to report worsening immediately; • If worsens, treat as Grade 2, 3 or 4.
Grade 2 • **Diarrhea:** 4 to 6 stools per day over Baseline; IV fluids indicated <24 hours; not interfering with ADL; • **Colitis:** abdominal pain; blood in stool.	• Withhold avelumab therapy; • Symptomatic treatment.	• If improves to Grade ≤1, resume avelumab therapy; • If persists >5-7 days or recurs, treat as Grade 3 or 4.
Grade 3 to 4 • **Diarrhea (Grade 3):** ≥7 stools per day over Baseline; incontinence; IV fluids ≥24 h; interfering with ADL; • **Colitis (Grade 3):** severe abdominal pain, medical intervention indicated, peritoneal signs; • **Grade 4:** life-threatening, perforation.	• Withhold avelumab for Grade 3; • Permanently discontinue avelumab for Grade 4 or recurrent Grade 3 • 1.0 - 2.0 mg/kg/day prednisone IV or equivalent; • Add prophylactic antibiotics for opportunistic infections; • Consider lower endoscopy.	• If improves, continue steroids until Grade ≤1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3); • If worsens, persists >3 to 5 days, or recurs after improvement, add infliximab 5 mg/kg (if no contraindication). *Note: infliximab should not be used in cases of perforation or sepsis.*

Table 7. Management of Immune-Related Adverse Events

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

Table 7. Management of Immune-Related Adverse Events

	hospitalization; • 1.0 - 2.0 mg/kg/day prednisone or equivalent; • Add prophylactic antibiotics for opportunistic infections; • Consider bronchoscopy, lung biopsy.	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 v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 • Grade 1 AST or ALT >ULN to 3.0 × ULN; • and/or Total bilirubin >ULN to 1.5 × 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 × ULN; • and/or total bilirubin >1.5 to ≤3 × ULN.	• Withhold avelumab therapy; • Increase frequency of monitoring to every 3 days.	• If returns to Grade ≤1, resume routine monitoring; resume avelumab therapy; • If elevation persists >5 to 7 days or worsens, treat as Grade 3 to 4.
Grade 3 to 4 • AST or ALT >5 × ULN; • and/or total bilirubin >3 × 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	• 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

Table 7. Management of Immune-Related Adverse Events

	clinically warranted.	local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased >ULN to 1.5 × 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 × 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 × 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.
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;	• Once improving, taper

Table 7. Management of Immune-Related Adverse Events

	• 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.	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 insufficiency, type I diabetes mellitus).	• Withhold avelumab therapy; • Consider hospitalization; • Endocrinology consult; • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate; • Rule-out secondary endocrinopathies (ie, hypopituitarism / hypophysitis).	• Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤1 (with or without hormone replacement/suppression); • Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
• **Hypopituitarism;** • **Hypophysitis (secondary endocrinopathies).**	If secondary thyroid and/or adrenal insufficiency is confirmed (ie, subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women); • Hormone replacement/suppressive therapy as appropriate;	• 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;

Table 7. Management of Immune-Related Adverse Events

	• 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.	• 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.
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.

Table 7. Management of Immune-Related Adverse Events

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 anti-tumor 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, by continuing to receive the investigational products, the patient may be foregoing approved or investigational therapies 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 RECIST v1.1 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. Reference Investigational Product Manual for storage and administration instructions.

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 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°C–8°C (36°F–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 AEs 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 is not permitted during the DLT observation period (eg, Cycle 1), but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guidelines.[45]

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 Treatment(s) 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.[46] 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.[48] 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 mCRPC

Patients with mCRPC 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, mistle toe 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.
- Strong P--gp inhibitors that result in ≥2-fold increase in the exposure of an in vivo probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/) are prohibited: amiodarone, carvedilol, clarithromycin, cobicistat, dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir, telaprevir, tipranavir, valspodar, and verapamil.

- 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.

The list of strong P-gp inhibitors and transporter inhibitors to be used with caution will be updated annually and reflected in the talazoaprib IB.[12]

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, where possible:

- Pharmacokinetic blood specimens – obtain at the scheduled time.
- Electrocardiograms (ECGs) – obtain as close as possible to the scheduled time (See Section 7.1.6).
- Blood pressure/pulse rate – may be obtained prior to or after ECG collection but must be obtained prior to blood specimen collection.
- 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/EOT

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

Patients may withdraw from treatment at any time at their own request, or they may be withdrawn 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. In this case, no further study specific 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. Subjects 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 post treatment study follow-up. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

6.3.2. 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 the Schedule of Activities and Section 7. All patients will be followed for safety every 30 days (±3 days) through 90 days after the last dose of study treatment or until the start of new anti-cancer treatment whichever occurs first.

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 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. For Long Term Follow-Up procedures, see the Schedule of Activities. 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 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, SAEs, vital signs, physical examination, 12-lead 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 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 patient 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, at the EOT visit, at the Day 30 Short Term Follow-Up 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)/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 8.4.2 and 8.4.2.1 for required pregnancy follow-up and safety reporting requirements and the Schedule of Activities for Short-Term and Long-Term Follow-Up procedures).

7.1.2. Contraception Check

Fertile male patients with female partners of reproductive potential or pregnant partners 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 the selected method of highly effective contraception. The investigator or his or her designee will discuss with the patient the need to use highly effective contraception preferably with low user dependence consistently and correctly during treatment and for the required period after the last dose of each study drug 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.

7.1.3. Adverse Events

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

7.1.4. Laboratory Safety Assessments

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at local laboratories. Required safety laboratory tests including at a minimum: hematology (hemoglobin, platelets, and white blood cells), chemistry (ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, and glucose), and pregnancy test (Day 1 only) results must be reviewed prior to study drug administration on Days 1 and 15 of each treatment cycle. If pregnancy tests are administered whenever 1 menstrual cycle is missed and when potential pregnancy is otherwise suspected, or if requested by IRBs/ECs, or if required by local regulations (Section 7.1.1), then pregnancy test results must also be reviewed prior to study drug administration on Day 15 for that treatment cycle.

The required safety laboratory tests are listed in Table 8.

Table 8. Required Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis (Dispstick is acceptable)	Pregnancy Test
Hemoglobin	ALT	INR	Urine dipstick for urine protein: If positive collect a microscopic sample (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 sample (Reflex Testing)	
Absolute Eosinophils	Chloride			
Absolute Basophils	Total Calcium			
	Total Bilirubin[a]			
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 mCRPC patients)*	Creatine Kinase			
	C-reactive Protein (CRP)			
	Lactate Dehydrogenase (LDH)			
	Lipase			

Abbreviations used in the table: ACTH=adrenocorticotropic hormone, ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, mCRPC=metastatic 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, RNA=ribonucleic acid, TSH=thyroid-stimulating hormone, WBC=white blood cell.

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

7.1.5. Physical Examinations and Vital Signs

Patients will have focused physical examinations to include major body systems, 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 the Schedule of Activities.

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

7.1.6. (12-Lead) Electrocardiograms

Triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. At each time point (see the Schedule of Activities), 3 consecutive ECGs will be performed approximately 2 minutes apart to determine mean QTc interval. When coinciding with PK blood sample draws, ECG assessment should be performed prior to blood sample collection, such that the blood sample is collected at the nominal time (ie, the timing of the PK collections overrides the timing of the ECG collections). On-treatment triplicate ECGs will be performed on Day 1 of Cycles 1 and 3, prior to PK collection at pre-dose (within 1 hour before administration of talazoparib) and post-dose (within 10 minutes after the end of avelumab infusion), at the EOT Visit and Short Term Follow-Up Visits (up to 90 days after the last dose of study treatment).

If the mean QTc is prolonged (>500 msec, ie, CTCAE Grade ≥3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational products, treatment may be continued with regular ECG monitoring as clinically indicated. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to ≤500 msec. Additional triplicate ECGs may be performed as clinically indicated.

If patient experiences any cardiac AE or syncope, dizziness, seizures, or stroke, triplicate ECGs should be obtained at time of the event.

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. Where noted in the Schedule of Activities, blood samples for avelumab and talazoparib concentrations will be collected immediately after triplicate 12-lead ECGs are performed. 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.

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).

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. 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. 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 ADAs, as outlined in the Schedule of Activities. 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 will 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:

- 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 a panel of DDR genes;

    - Genomic scarring as assessed by LOH;

    - 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. DDR Defect Sample

All patients must provide a tumor tissue sample to the Foundation Medicine central laboratory for testing of DDR defects via the Foundation One assay or validated local assay result. Tumor tissue from cytologic sampling (eg, fine needle aspiration, including FFPE cell pellet material) or from bone biopsies is not adequate and should not be submitted.

Tissue should be sent in the form of 15 unstained slides, positively charged and unbaked at 4-5 microns thick, and one original (not recut) H&E slide. The portion of the tumor used should optimally measure 5×5 mm and contain minimally 20% and optimally 40% or greater tumor nuclei.

The slides should be taken from an FFPE tumor tissue sample, which was obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment, during which time the patient should have received no more than one line of systemic anti-cancer therapy.

In instances where no such sample is available a biopsy from a locally recurrent or metastatic tumor site that is not the only RECIST v1.1 target lesion must be performed during screening. For mCRPC patients with no lesion that can be biopsied outside of bone at screening, tumor tissue from a biopsy/surgery performed within 5 years prior to study enrollment must be submitted without repeating a tumor biopsy during the screening period. For patients who require prospective biomarker testing as part of the eligibility criteria, including NSCLC Cohort A2, HR+/HER2- breast cancer Cohort B2, and mCRPC Cohort E2, the biopsy may be performed within 45 days prior to enrollment.

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

7.4.1.2. Baseline Tumor Tissue Samples

In additionto the 15 slides described above in Section 7.4.1.1, all patients must submit an FFPE tumor tissue block to support the biomarker analyses outlined above. This tissue block must be obtained from a biopsy or surgery that was performed within 2 years prior to study enrollment, during which time the patient should have received no more than one line of systemic anti-cancer therapy. In instances where no such sample is available a biopsy must be performed during screening, as described above in Section 7.4.1.1. For mCRPC patients with no lesion that can be biopsied outside of bone at screening, tumor tissue from a biopsy/surgery performed within 5 years prior to study must be provided.

Where documented local or institutional regulations prevent the submission of tissue blocks, then a minimum of 10 slides must be submitted.

7.4.1.3. On Treatment and End of Treatment Tumor Tissue Samples

Additionally, optional on- treatment tumor biopsies are encouraged between Cycle 1 Day 15 and Cycle 3 Day 1.

Tumor tissue is also requested for those patients who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period.

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 poses an unacceptable risk to patients in the clinical research setting. A 14-day window is permitted.

7.4.1.4. Archival Tumor Tissue Samples

For patients who have an older archive tissue sample, obtained from a surgery or biopsy performed greater than 2 years prior to enrollment, an FFPE tumor tissue block, or 5-10 unstained slides, from this tissue sample must be submitted if available.

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 pre and post treatment.
- Blood sample (20 mL whole blood) will be collected for processing to plasma for ctDNA isolation and subsequent analysis of genetic biomarkers that may relate to response.
- Blood samples (4 mL and 10 mL for processing to plasma and serum, respectively) will be collected to assess proteomic and metabolomic factors and signatures pre-dose.
- Blood samples (2 × 2.5 mL) will be collected and processed to generate RNA. RNA will be used to assess the level of expression of genes in peripheral blood at screening, during treatment, and after treatment discontinuation.
- A single blood sample (4 mL) will be collected and processed to generate DNA. DNA will be used to assess potential epigenetic or genetic biomarkers that may relate to response to treatment.

7.4.3. Additional Analyses

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

It is possible that the use of these biospecimens may result in commercially viable products. Subjects 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 patients with the specified tumor types, except mCRPC, will undergo 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 year 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 1 year from the start of the study treatment, and then every 16 weeks thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy, as specified in the Schedule of Activities, 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 according to RECIST v1.1, 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). Details of treatment after initial evidence of radiological disease progression are provided in Section 5.4.7.

All patients' files and radiologic images must be available for source verification and for potential peer review. All radiographic images will be collected and stored by an independent third-party imaging laboratory, according to instructions provided in the Imaging Manual.

7.6.1. mCRPC Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging 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. 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. Bone scans must be performed at every tumor assessment.

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, 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.[43] The documentation required for the determination of radiographic progression is shown in Appendix 5.

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 5 for the timing of confirmatory imaging requirements.

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

All patients' files and radiologic images must be available for source verification and for potential peer review. All radiographic images will be collected and stored by an independent third-party imaging laboratory, according to instructions provided in the Imaging Manual.

7.7. Blood Tests for Tumor Markers

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 and analyzed at local laboratories for cancer antigen 125 (CA-125) testing to monitor the patient's disease. Elevated CA-125 test results should trigger a radiological tumor assessment due to suspected disease progression.

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 and analyzed at local laboratories for prostate-specific antigen (PSA) to monitor the patient's disease. Elevated PSA test results should trigger a radiological tumor assessment due to suspected disease progression.

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) SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious 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 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/EOT 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

An SAE 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 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. 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 × 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.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, 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.

8.4.2. 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.

8.4.2.1. 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.

8.4.2.2. Exposure During Breastfeeding

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

8.4.2.3. Occupational Exposure

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

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a 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.

8.4.3. 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

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 is 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. Evaluable for DLT Analysis Set

The DLT analysis set is a subset of the safety analysis set and includes all enrolled patients in the Phase 1b portion who are eligible for the study, receive at least one dose of the combination treatment, and either experience DLT during the first cycle (28 days) of treatment, or complete the DLT observation period for the first cycle of treatment.

Patients without DLTs who withdraw from study treatment before receiving at least 75% of the planned dose of each of the investigational products in the combination in Cycle 1 for reasons other than toxicity which are attributable to the investigational products are not evaluable for DLT. Additional patients will be enrolled in the specific cohort to replace patients who are not considered DLT evaluable.

9.1.4. Pharmacokinetics/Immunogenicity Analysis Set

9.1.4.1. Pharmacokinetics Analysis Set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least 1 concentration above the 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.

9.1.4.2. Immunogenicity Analysis Set

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

9.1.4.3. Biomarker Analysis Set

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

9.2. Statistical Methods and Properties

9.2.1. Phase 1b

Before expanding into Phase 2, the safety must be confirmed in the first 12 patients evaluable for DLT treated at the same dose level.

A safe dose will be determined using the adaptive mTPI design. The mTPI design is flexible and allows dose reduction to doses in between the planned doses.

The mTPI design uses a Bayesian statistics framework and a beta/binomial hierarchical model to compute the posterior probability of 3 dosing intervals that reflect the relative difference between the toxicity rate of each dose level to the target probability (pT) rate (pT=0.25). If the toxicity rate of the currently used dose level is far smaller than pT, the mTPI will recommend escalating the dose level; if it is close to pT, the mTPI will recommend continuing at the current dose; if it is far greater than pT, the mTPI will recommend de-escalating the dose level. These rules are conceptually similar to those used by the 3+3 design, except the decisions of an mTPI design are based on posterior probabilities calculated under a coherent probability model. As shown by Ji and Wang, mTPI design is more efficient and safer than the 3+3 design.[49] They considered 42 scenarios to cover a wide range of practical dose-response shapes, and concluded that the 3+3 design was more likely to treat patients at toxic doses above the MTD and less likely to identify the true MTD than the mTPI design. For example, the 3+3 design exhibited a lower overall toxicity percentage than the mTPI design in only 1 of 42 scenarios.

Being a model-based design, mTPI automatically and appropriately tailors dose re-escalation and de-escalation decisions for different studies with different toxicity parameters. More importantly, all the dose re-escalation/de-escalation decisions for a given study can be pre-calculated under the mTPI design and presented in a 2-way table. Thus, compared to other advanced model-based designs published in the literature, the mTPI design is logistically less complicated and easier to implement.

Decision rules are based on calculating unit probability mass (UPM) of 3 dosing intervals corresponding to under, proper, and overdosing in terms of toxicity. Specifically, the underdosing interval is defined as (0, pT-e1), the overdosing interval (pT+e2, 1), and the proper-dosing interval (pT- e1, pT+ e2), where e1 and e2 are small fractions. Based on the safety profile of talazoparib and avelumab, e1 is selected as 0.09, and e2 is selected as 0.08. Therefore, the target interval for the DLT rate is (0.16, 0.33).

The 3 dosing intervals are associated with 3 different dose-escalation decisions (see Section 3.1.1.1). The underdosing interval corresponds to a dose re-escalation (E), overdosing corresponds to dose de-escalation (D), and proper dosing corresponds to staying at the current dose (S). Given a dosing interval and a probability distribution, the UPM of that dosing interval is defined as the probability of a patient belonging to that dosing interval divided by the length of the dosing interval. The mTPI design calculates the UPMs for the 3 dosing intervals, and the one with the largest UPM informs the corresponding dose-finding decision, which is the dose level to be used for future patients. For example, if the

underdosing interval has the largest UPM, the decision will be to escalate, and the next cohort of patients will be treated at the next higher dose level. Simulations have demonstrated that the decision based on UPM is optimal in that it minimizes a posterior expected loss (ie, minimizes the chance of making a wrong dosing decision).

The Phase 1b evaluation is completed when 12 DLT-evaluable patients have been treated at the highest dose levels associated with a DLT rate <0.33 or if the combinations are deemed too toxic, as determined by the DLT rate and/or lower than expected doses of the study treatments.

Early completion of Phase 1b may occur if 9 or more DLT-evaluable patients have been treated at the same dose level with no occurrence of DLT, as the DLT rate of <0.33 will be met.

9.3. Sample Size Determination

Due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI design cannot be determined in advance. It is expected that 12-36 patients will need to be enrolled in Phase 1b using the mTPI design.

Phase 2 expansion cohorts will enroll up to approximately 10, 20 or 40 patients (cohort-specific as shown in Figure 3.

Table 9 provides the exact binomial 90% CIs for ORR based on different observed responses in a cohort.

Table 9. Sample Size and Exact 90% Confidence Intervals for ORR

N per Cohort	Number of Responders	Observed ORR	90% CI for ORR
10	1	10%	(0.5% - 39.4%)
	2	20%	(3.7% - 50.7%)
	3	30%	(8.7% - 60.7%)
	4	40%	(15.0% - 69.6%)
	5	50%	(22.2% - 77.8%)
	6	60%	(30.4% - 85.0%)
20	1	5%	(0.3% – 21.6%)
	2	10%	(1.8% – 28.3%)
	3	15%	(4.2% – 34.4%)
	4	20%	(7.1% – 40.1%)
	5	25%	(10.4% – 45.6%)
	6	30%	(14.0% – 50.8%)
	7	35%	(17.7% – 55.8%)
	8	40%	(21.7% – 60.6%)
	9	45%	(25.9% – 65.3%)
	10	50%	(30.2% – 69.8%)
	12	60%	(39.4% – 78.3%)
	15	75%	(54.4% – 89.6%)
40	2	5%	(0.9% – 14.9%)
	4	10%	(3.5% – 21.4%)
	6	15%	(6.7% – 27.5%)
	8	20%	(10.4% – 33.2%)

Table 9. Sample Size and Exact 90% Confidence Intervals for ORR

N per Cohort	Number of Responders	Observed ORR	90% CI for ORR
	10	25%	(14.2% – 38.7%)
	12	30%	(18.3% – 44.0%)
	14	35%	(22.6% – 49.2%)
	16	40%	(26.9% – 54.2%)
	18	45%	(31.5% – 59.1%)
	20	50%	(36.1% – 63.9%)
	24	60%	(45.8% – 73.1%)
	30	75%	(61.3% – 85.8%)
	35	87.5%	(75.5% – 94.9%)

Abbreviations: CI=confidence interval; ORR=objective response rate

9.3.1. Cohorts A1 and A2

Cohorts A1 and A2 will enroll patients with NSCLC.

Cohort A1: Up to approximately 40 patients will be enrolled.

Cohort A2: Up to approximately 20 patients who are anti-PD-L1 resistant and DDR Defect + will be enrolled.

With approximately 40 patients in a cohort, ORR can be estimated with a maximum standard error of 0.079.

9.3.2. Cohorts B1 and B2

Cohort B1 will enroll up to approximately 20 patients with TNBC and Cohort B2 will enroll up to approximately 20 patients with HR+/HER2- breast cancer and DDR Defect +.

With approximately 20 patients in a cohort, ORR can be estimated with a maximum standard error of 0.112.

9.3.3. Cohorts C1 and C2

Cohorts C1 and C2 will enroll patients with platinum-sensitive recurrent ovarian cancer. Up to approximately 20 patients with a BRCA defect will be enrolled. With approximately 20 patients, ORR can be estimated with a maximum standard error of 0.112.

9.3.4. Cohort D

Up to approximately 40 patients with UC will be enrolled. With approximately 40 patients, ORR can be estimated with a maximum standard error of 0.079.

9.3.5. Cohorts E1 and E2

Cohorts E1 and E2 will enroll patients with mCRPC.

Cohort E1: Up to approximately 20 patients will be enrolled.

Cohort E2: Up to approximately 20 patients with DDR Defect + will be enrolled.

With approximately 20 patients in a cohort, ORR can be estimated with a maximum standard error of 0.112.

9.3.6. Cohort F

Up to approximately 10 patients will be enrolled in Cohort F. With 10 patients, ORR can be estimated with a maximum standard error of 0.158.

9.4. Efficacy Analysis

All efficacy analyses will be performed based on the full analysis set, separately by dose level and for all dose levels combined in Phase 1b and by cohort in Phase 2.

In the definitions below, start date refers to the date of first dose of study treatment for all cohorts.

Summaries for efficacy endpoints in patients with mCRPC in Cohort F will be tabulated only if >3 patients with mCRPC in Cohort F receive study drug.

9.4.1. Analysis of the Primary Endpoint

The primary endpoint for Phase 2 is confirmed OR. The definitions and analyses below apply to patients with locally advanced or metastatic solid tumors in Phase 1b.

- For patients with solid tumors, except mCRPC (Cohorts A1, A2, B1, B2, C1, C2, D, and F):

OR is defined as a CR or PR per RECIST v1.1 by Investigator 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 per Investigator's assessment 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 two-sided exact 90% and 95% CIs for ORR will be calculated.

- For patients with mCRPC (Cohorts E1, E2, and F):

OR is defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST v1.1 by Investigator 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 by Investigator. 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 5).[43]

9.4.2. Analysis of the Secondary Endpoints

For patients with solid tumors, except mCRPC (Cohorts A1, A2, B1, B2, C1, C2, D, and F):

- 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 start date 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 their 90% and 95% CIs.

For patients with mCRPC (Cohorts E1, E2, and F):

- 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 as assessed by Investigator using 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) as assessed by Investigator using 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 as assessed by Investigator using RECIST v1.1 or bone disease progression as assessed by Investigator using PCWG3 (see Appendix 5).

- PFS is defined as the time from the first dose of study treatment to documentation of radiographic progression in soft tissue as assessed by Investigator using RECIST v1.1, in bone as assessed by Investigator using PCWG3, or death, whichever occurs first (see Appendix 5). 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 the 90% and 95% CIs.

- Time to PSA progression for patients with mCRPC 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 their 90% and 95% CIs.

For patients with ovarian cancer (Cohorts C1 and C2):

- 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.

9.5. Analysis of Pharmacokinetics and Pharmacodynamics

9.5.1. 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 Cycles 2-4 for both talazoparib and avelumab, and additionally on Day 1 of Cycles 6, 9, 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 by dose level in Phase 1b and by cohort in Phase 2. 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 in Phase 2, as well as combined across all patients in Phase 2 with patients in the RP2D dose

level in Phase 1b. 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.

9.5.2. 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.

9.5.3. Analysis of Biomarker Secondary and Exploratory Endpoints

All analyses of biomarkers will be performed based on the biomarker analysis set, separately by dose level and for all dose levels combined in Phase 1b and by cohort in Phase 2.

Biomarker data will include baseline and on-treatment expression levels of protein markers associated with target and immune cell phenotypes of interest including, but not limited to, PD-L1 expression in tumor tissue, presence of defects in DDR-related genes, presence of genomic scarring, and TMB.

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/EOT time points, as appropriate.

Appropriate change from baseline measurements will be provided. For discrete measurement biomarkers, frequencies and percentages of categorical biomarker measures will be 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 Wilcoxon signed-rank test, Wilcoxon rank-sum test, correlation/linear regression, box-and-whisker plots, etc. The statistical approaches will examine correlations of biomarker results with pharmacokinetic parameters and measures of efficacy, such as tumor response and progression free survival.

9.5.4. Analysis of Immunogenicity Data of Avelumab

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

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. A comparison of safety and efficacy endpoints between avelumab ADA and Nab positive vs. negative patients may be performed, if data permit.

9.6. Safety Analysis

All safety analyses will be performed based on the safety analysis set, separately by dose level in Phase 1b and by cohort in Phase 2 and for all patients in the Phase 1b and Phase 2 combined.

9.6.1. Analysis of the Primary Endpoint in Phase 1b

DLT is the primary endpoint for Phase 1b.

Analyses of DLT are based on the DLT-evaluable set. The occurrence of DLTs and AEs constituting DLTs will be summarized and listed per cohort, overall and by dose level, for patients enrolled in Phase 1b.

9.6.2. 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.

9.6.3. 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.

9.6.4. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data. Baseline is defined as pre-dose triplicate ECG assessment obtained on Day 1 of Cycle 1. ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (QTc) using standard correction factors [ie, Fridericia's (default correction), Bazett's, and possibly a study specific factor, as appropriate]. Data will be summarized and listed for QT, HR, RR, PR, QRS, and QTc. Individual QT (all evaluated corrections) intervals will be listed by cohort and timepoint. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers, and used for the study conclusions.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by cohort and time point. The maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post baseline corrected QT interval.

Shift tables will be provided for baseline versus worst on treatment corrected QT (one or more correction method will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline versus on treatment (yes, no, not done: [n, %]). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of talazoparib and avelumab drug concentrations on corrected QT change from baseline will be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models.

9.7. 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.

9.8. Interim Analysis

No formal interim analysis will be conducted for this study. However, 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 dose-finding decisions, facilitating PK/Pharmacodynamic modeling, and/or to support clinical development.

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's chart. In these cases, data collected on the CRFs must match the data in those charts.

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating 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 must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in 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.

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Appendix 1. Abbreviations and Definitions of Terms

The following is a list of abbreviations that are 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 Plasma Concentration-Time Curve
BBS	Biospecimen Banking System
BCRP	Breast Cancer Resistance Protein
BOR	Best Overall Response
BP	Blood Pressure
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
BRCA	BReast CAncer Susceptibility Gene
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CA-125	Cancer Antigen 125
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CrCl	Creatinine Clearance
CL/F	Apparent Oral Clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
C_{trough}	Mean Plasma Trough Concentration
CR	Complete Response
CRF	Case Report Form
CRP	C-Reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CYP450	Cytochrome P450
D	Dose

DDI	Drug-Drug Interaction
DDR	DNA Damage Repair
DILI	Drug-Induced Liver Injury
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
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
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GITR	Glucocorticoid Induced TNF Receptor
GnRH	Gonadotropin-Releasing Hormone
GVHD	Graft Versus Host Disease
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HR+	Hormone Receptor Positive
HRD	Homologous Recombination Deficiency
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICOSL	Inducible Costimulator Ligand
ID	Identification
IDO	Indoleamine 2,3-Dioxygenase
IERC	Independent Endpoint Review Committee
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-2	Interleukin-2
IND	Investigational New Drug
INR	International Normalized Ratio

IP	Investigational Product
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
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
MCC	Merkel Cell Carcinoma
mCRPC	Metastatic Castration-Resistant Prostate Cancer
M-CSF	Macrophage-Colony Stimulating Factor
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Compex
mPDAC	Metatstatic Pancreatic Ductal Adenocarcinoma
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
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PBMC	Peripheral Blood Mononuclear Cell
PCD	Primary Completion Date
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
PET	Positron Emission Tomography
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PMAP	Pharmacometric analysis plan
PR	Partial Response
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 Dose
S	Stay (at current dose)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SRSD	Single Reference Safety Document
STING	Stimulation of Interferon Genes
$t_{1/2}$	Terminal Half-Life
TBili	Total Bilirubin
TCR	T-cell Receptor
TDO	Tryptophan 2,3-Dioxygenase
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Maximum Plasma Concentration
TMB	Tumor mutational burden
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
VEGF	Vascular Endothelial Growth Factor
V_{ss}/F	Apparent Steady-State Volume of Distribution

V/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

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.[50]

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.[51]

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 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 EOT 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. Detailed Dose Escalation/De-Escalation Scheme for mTPI Design

Number of dose limiting toxicities (DLTs)	Number of patients treated at current dose									
	3	4	5	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	E	E	E	E	E
2	D	D	S	S	S	S	S	S	S	S
3	DU	DU	DU	D	S	S	S	S	S	S
4		DU	DU	DU	DU	DU	D	S	S	S
5			DU	DU	DU	DU	DU	DU	D	S
6				DU	DU	DU	DU	DU	DU	DU
7					DU	DU	DU	DU	DU	DU
8						DU	DU	DU	DU	DU
9							DU	DU	DU	DU
10								DU	DU	DU
11									DU	DU
12										DU

E = Escalate to the next higher dose (if a higher dose level is available); otherwise remain at the current dose.
S = Stay at the current dose.
D = De-escalate to the next lower dose level (if a lower dose level is available).
U = The current dose is unacceptably toxic and it will not be tested further.
Target DLT rate at MTD = 0.25.

Escalation/De-escalation algorithms for total number of patients treated at the current dose level (current and previous cohorts):

- With 3 patients treated at current dose level:
  - 0 DLT → escalate;
  - 1 DLT → remain at the same dose;
  - 2 DLTs → de-escalate ;
  - 3 DLTs → de-escalate and consider current dose as intolerable.
- With 4 patients treated at current dose level:
  - 0 DLT → escalate;
  - 1 DLTs → remain at the same dose;

- 2 DLTs → de-escalate;
- 3-4 DLTs → de-escalate and consider current dose as intolerable.

- With 5 patients treated at current dose level:
  - 0 DLT → escalate;
  - 1-2 DLTs → remain at the same dose;
  - 3-5 DLTs → de-escalate and consider current dose as intolerable.
- With 6 patients treated at current dose level:
  - 0 DLT → escalate;
  - 1-2 DLTs → remain at the same dose;
  - 3 DLTs → de-escalate;
  - 4-6 DLTs → de-escalate and consider current dose as intolerable.
- With 7 patients treated at current dose level:
  - 0 DLT → escalate;
  - 1-3 DLTs → remain at the same dose;
  - 4-7 DLTs → de-escalate and consider current dose as intolerable.
- With 8 patients treated at current dose level:
  - 0-1 DLT → escalate;
  - 2-3 DLTs → remain at the same dose;
  - 4-8 DLTs → de-escalate and consider current dose as intolerable.
- With 9 patients treated at current dose level:
  - 0-1 DLT → escalate;
  - 2-3 DLTs → remain at the same dose;
  - 4 DLTs → de-escalate;
  - 5-9 DLTs → de-escalate and consider current dose as intolerable.

- With 10 patients treated at current dose level:
  - 0-1 DLT → escalate;
  - 2-4 DLTs → remain at the same dose;
  - 5-10 DLTs → de-escalate and consider current dose as intolerable.
- With 11 patients treated at current dose level:
  - 0-1 DLT → escalate;
  - 2-4 DLTs → remain at the same dose;
  - 5 DLTs → de-escalate;
  - 6-11 DLTs → de-escalate and consider current dose as intolerable.
- With 12 patients treated at current dose level:
  - 0-1 DLTs → escalate;
  - 2-5 DLTs → remain at the same dose;
  - 6-12 DLTs → de-escalate and consider current dose as intolerable.

Appendix 5. Assessment of Radiographic Response and Progression in Patients with mCRPC

Radiographic imaging for patients with mCRPC 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.

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.[43] 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.