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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STATISTICAL ANALYSIS PLAN – B9991025

Compounds:	MSB0010718C MDV3800, BMN 673
Compound Name:	Avelumab Talazoparib
Version:	3.0
Date:	16-Dec-2021

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991025 is based on the protocol amendment 03 dated 20NOV2018.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
3	16-Dec-2021	The following changes were implemented: • Section 2. "Introduction" – The definition of the primary analysis cutoff date was modified to allow longer patient follow-up. • Section 6.2.3. "Pharmacokinetic endpoints" – A criterion was added to clarify the exclusion from analyses of data for which time of collection cannot be confirmed. [redacted] • Section 6.6.1.3. "Adverse events leading to interruption of study treatment" - The summary tables and listing of TEAEs leading to interruption of each study drug (avelumab, talazoparib) were deleted. • Section 6.6.1.1. "All adverse events" and Section 6.6.1.3. "Adverse events leading to discontinuation of study treatment" - The summary tables of TEAEs leading to permanent discontinuation of each study drug (avelumab, talazoparib) were deleted. • Section 6.6.4. "Other significant adverse events" - The summary tables of irAEs leading to discontinuation of each study drug (avelumab, talazoparib), any, and all drugs and the summary tables of IRRs leading to discontinuation of avelumab, and time related to first onset of an IRR were deleted. • Section 6.6.5.1. "Hematology and chemistry parameters" – The shift tables for the parameters with NCI-CTCAE grades available and the eDISH plot were deleted. The Hy's Law criteria for the listing was corrected, • Section 6.6.6. "Vital signs" - The vital sign summaries by visit were deleted. • Section 6.6.6. "Electrocardiogram" – Pearson correlation was deleted.
2	22-Sep-2020	The following changes in the SAP were implemented in accordance to protocol amendment 3. • Section 2.1. "Study Objectives", [redacted] analyses associated with irRECIST were deleted. • Section 2.2. "Study Design", Section 3.4.1. "Study drug, study treatment and baseline definitions", Section 5.2. "General Methods" – Cohorts A2 and B2 eligibility criteria was changed; cohort F was added. The target enrollment of Cohort A2 was reduced to up to approximately 20 as the patient population has changed and this cohort is now only exploratory, Cohort C1 size was reduced to up to approximately 20, In addition, the following changes were implemented. • Section 3.2.3. "Pharmacokinetic endpoints" – 'plasma' was removed from Cmax definition as avelumab Cmax was measured in serum. Tmax will not be reported as Tmax is at the end of the avelumab IV infusion administration. The method of determining the actual time difference for

		avelumab and talazoparib post-dose samples relative to dosing were clarified. • Section 3.4.2. "Baseline characteristics", Section 5.2.8. "Standard derivations and reporting conventions", Section 6.5.1.1. "Demographic characteristics" – the summary of physical measurements (BMI, height and weight) was deleted. • Section 3.5.1. "Adverse events – the definition of treatment-emergent adverse events was updated to include only adverse events that start during the on-treatment period. • Section 4.3.2. "PK analysis sets" – the definition of the PK parameter analysis set was clarified to be the same as the PK concentration analysis set.. • Section 5.1.1. "Hypotheses and sample size determination" – sample size of 10 patients was added in Table 4 for Cohort F. • Section 5.1.1 "Hypotheses and sample size determination", Section 6.2.3. "Pharmacokinetic endpoints" – since PK analysis will be run on all patients in Phase1b and Phase 2 combined, Table 5 was updated. Redundant explanations on the analyses were simplified. Analysis on patients who have undergone dose escalation was removed as it is not allowed per protocol. Drug-drug interactions will be analyzed using modeling approaches instead of comparison with the historical PK parameters with description moved to Section 6.2.4 "Population pharmacokinetic endpoints. • Section 5.1.1. "Hypotheses and sample size determination", Section 6.2.6. "Endpoints for immunogenicity data of avelumab and talazoparib" – immunogenicity analysis will be run on all patients in Phase 1b, in Phase 2 and in Phase1b and Phase 2 combined, Table 5 was updated. • Section 6.1.2. "Objective response as assessed by the Investigator per RECIST v1.1" – added "No evidence of disease at baseline" as a possible reason for best overall response of NE as applicable to patients with mCRPC with no measurable disease and no non-target lesions at baseline. • Section 6.2.2.2. "Duration of response" – added details regarding censoring for duration of response since "no adequate baseline assessment" and "no adequate post-baseline assessment" which is used in censoring for PFS analyses is not applicable to analyses of duration of response for patients with objective response. The listing of duration of response time was removed. • Section 6.2.2.4. "Progression-free survival" - the summary of time of follow-up for PFS was simplified. • Section 6.2.2.5 "Overall survival" - the summary of time of follow-up for OS was simplified. • Section 6.2.2.7. "PSA response for patients with metastatic CRPC" – the plot of the percent change in PSA value from baseline and best percentage change in PSA value from baseline were added. • Section 6.2.3. "Pharmacokinetic endpoints" – redundant explanations on the analyses were simplified. Analysis on patients who have undergone dose escalation was removed as it is not allowed per protocol. Drug-drug interactions will be analyzed using modeling approaches instead of comparison with the historical PK parameters with description moved to Section 6.2.4 "Population pharmacokinetic endpoints.

		• Section 6.2.5. "Biomarker endpoints", CCI [redacted] CCI [redacted] Table 5 – analysis on full analysis set was added to include the category of patients with unknown biomarker status. • Section 6.2.6. "Endpoints for immunogenicity data of avelumab and talazoparib" – ADA and nAb categories are described in Table 14 and Table 15. • Section 6.5.1.3. "Disease characteristics" - the summary of substance use was removed. • Section 6.5.1.4. "Prior anti-cancer therapies", Section 6.5.5. "Subsequent anti-cancer therapies" - the listings of anti-cancer radiation therapy and anti-cancer surgeries were removed. • Section 6.5.2.1. "Patient disposition" – a cross-tabulation of patient disposition was added. • Section 6.5.3.1. "Exposure to avelumab" - removed by-cycle summaries. • Section 6.5.3.4. "Dose interruptions" – the reason for dose interruption was removed from the analysis specifications. • Section 6.5.4. "Concomitant medications and non-drug treatments" - the summaries of prior medications and pre-medications and the listings of prior medications, concomitant medications, pre-medications and non-drug treatments were removed. • Section 6.6.1 "Adverse events" and subsections – the following summaries were removed: adverse events leading to dose reduction of avelumab (avelumab dose reduction is not allowed per protocol), adverse events excluding serious adverse events, adverse events leading both dose reduction and interruption of avelumab or talazoparib, adverse events leading to both interruption and dose reduction. • Section 6.6.1 "Other significant adverse events" – the related irAEs and related IRRs were removed. • Section 6.6.5.1. "Hematology and chemistry parameters" - the summary of laboratory parameters by CTCAE grade table was replaced by the summary of newly occurring or worsening laboratory abnormalities. • Section 6.6.6 "Electrocardiogram" – the summary of ECG parameters by timepoint was removed. • Section 6.6.8. "Physical Examination" was removed as no data were collected in the eCRF. • Section 6.6.9. "ECOG performance status" - the ECOG shift table was removed. • Appendix 1 "Immune-Related Adverse Events" - steps 3 and 4 of the algorithm will be checked concurrently. • Redundant listings or listings that do not provide meaningful information were removed. • Throughout this document 'start date' was replaced by 'date of first dose of study treatment'. • Minor editorial and consistency changes throughout the document.
1	22-Aug-2017	Not applicable (N/A)

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991025. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, pharmacokinetics data [PK], immunogenicity data, biomarker data). The primary analysis will include all data up to a cut-off date corresponding to at least 18 months after the last patient is receives the first dose of study drug. The final analysis of the data will be performed after last patient last visit (LPLV).

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

2.1. Study Objectives

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 Objective Response Rate (ORR) of avelumab in combination with talazoparib, as assessed by the Investigator, per Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 in patients with locally advanced or metastatic solid tumors and per RECIST v1.1 and Prostate Cancer Working Group 3 (PCWG3) in patients with metastatic Castration-Resistant Prostate Cancer (CRPC).

Secondary Objectives

- To assess the overall safety and tolerability of avelumab in combination with talazoparib;
- To characterize the pharmacokinetics (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 Programmed Death-Ligand 1 (PD-L1) expression and with potential biomarkers of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor sensitivity in baseline tumor tissue.

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2.2. Study Design

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 non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), hormone receptor positive HER2 negative (HR+/HER2-) breast cancer, recurrent platinum-sensitive ovarian cancer, urothelial 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.

The study design, including the number of patients to be enrolled into each cohort, is shown in Figure 1.

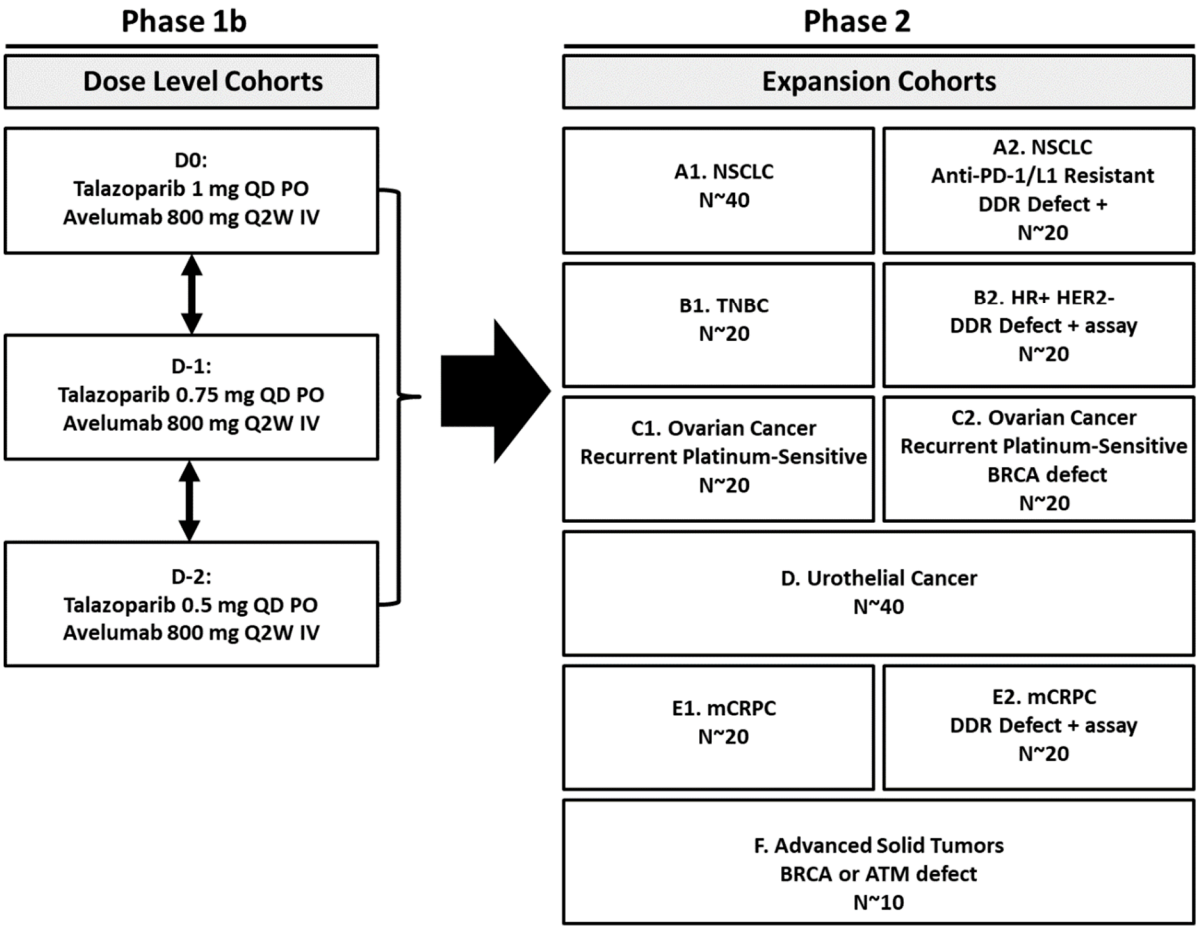
Phase 1b

In Phase 1b, 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 (1.0 mg, 0.75 mg or 0.5 mg) administered orally once daily (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. The starting dose level will be 1.0 mg talazoparib QD plus 800 mg avelumab Q2W. The dose levels of the combination to be evaluated are as follow:

- D0: talazoparib 1 mg PO QD in combination with avelumab 800 mg IV Q2W
- D-1: talazoparib 0.75 mg PO QD in combination with avelumab 800 mg IV Q2W
- D-2: talazoparib 0.5 mg PO QD in combination with avelumab 800 mg IV Q2W

where IV=intravenously; PO=orally; QD=once daily; Q2W=every 2 weeks.

Figure 1. 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.

Approximately 12-36 patients are expected to be enrolled in Phase 1b using the mTPI method (see Section 5.1).

Phase 2

All available data (including safety and preliminary anti-tumor activity) emerging from Phase 1b will be evaluated before starting enrollment of patients in Phase 2. The Phase 2 portion of this study will further assess the safety and preliminary anti-tumor activity of the avelumab in combination with talazoparib at the RP2D. Cohorts in Phase 2 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.

Up to approximately 230 patients are expected to be enrolled in Phase 2.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Phase 1b: DLT during the DLT evaluation period (Cycle 1).

  Severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In the Phase 1b, 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 study drugs 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: Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) >3×Upper Limit of Normal (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 (AP) <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.

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.

- Phase 2: 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 metastatic CRPC.

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first dose of study treatment until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety 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.

  AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing.

3.2.2. Efficacy endpoints

- 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 metastatic CRPC;

- 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 metastatic CRPC, time to prostate-specific antigen (PSA) progression for patients with metastatic CRPC, and overall survival (OS);

  DR is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

  TTR is defined, for patients with an OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

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

  Time to PSA progression for patients with metastatic CRPC is defined as the time from the date of first dose of study treatment 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. PSA progression must be confirmed by a second, consecutive PSA assessment ≥3 weeks later.

  OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause.

- PSA response ≥50% for patients with metastatic CRPC.

  PSA response is defined as PSA decline ≥50% compared to baseline. PSA response must be confirmed by a second, consecutive PSA assessment ≥ 3 weeks later.

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

  CA-125 response is defined as ≥ 50% reduction in CA-125 levels from baseline. CA-125 response must be confirmed by a second, consecutive CA-125 value ≥ 4 weeks later.

3.2.3. Pharmacokinetic endpoints

- PK parameters for avelumab and talazoparib including: pre-dose/trough concentrations (C_{trough}) and post-dose concentrations for talazoparib and maximum concentrations (C_{max}) for avelumab.

Table 2. PK Parameters to be Determined for Avelumab and Talazoparib

Parameter	Definition	Method of Determination
C_{max} [a]	Maximum observed concentration (=End of Infusion (EOI) for avelumab)	Observed directly from data
C_{trough}	Predose concentration during multiple dosing	Observed directly from data

[a] For avelumab only.

For avelumab, the actual time difference between avelumab infusion start time (for pre-dose) and end time (for post-dose) will also be reported.

For talazoparib, the post-dose concentration, taken at the end of avelumab infusion, and its actual time relative to talazoparib dose will also be reported, when appropriate.

3.2.4. Immunogenicity endpoints

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

3.2.5. Biomarker endpoints

- PD-L1 expression level in baseline tumor tissue.
- Genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue.

Table 3. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression level in baseline tumor tissue	The number of PD-L1 positive cells and/or qualitative assessment of PD-L1 staining on tumor and inflammatory cells in regions of interest	Pathologist, assisted by image analysis.
Genomic scarring and the presence of defects in select genes, considered critical to effective DDR, in baseline tumor tissue	Quantitation of genomic scarring in the form of genomic loss of heterozygosity; The number of mutations present in a panel of genes associated with DDR.	Next generation sequencing followed by computational analysis.

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3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

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

- Dose level cohort D0 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 1 mg QD PO;
- Dose level cohort D-1 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 0.75 mg QD PO;
- Dose level cohort D-2 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 0.5 mg QD PO;
- Cohort A1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with NSCLC;
- Cohort A2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with NSCLC and PD-1/L1 resistant and DDR Defect +;
- Cohort B1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with TNBC;
- Cohort B2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with HR+/HER2- breast cancer and DDR Defect + assay;
- Cohort C1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with recurrent platinum-sensitive ovarian cancer;
- Cohort C2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with recurrent platinum-sensitive ovarian cancer and BRCA defect;
- Cohort D (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with UC;
- Cohort E1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with CRPC;
- Cohort E2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with CRPC and DDR defect+ assay;
- Cohort F (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with advanced solid tumor with a germline or somatic BRCA1, BRCA2 or ATM gene defect.

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for efficacy analyses and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety for safety and efficacy analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and Appendix 2, respectively.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first study treatment received.

4.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one study treatment, the patient will be classified according to the first study treatment received. In this non-randomized study, the FAS and the safety analysis set are identical.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

The DLT analysis set is a subset of the safety analysis set and includes all enrolled patients in the Phase 1b 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 study drugs in the combination in Cycle 1 for reasons other than toxicity which are attributable to the study drugs are not evaluable for DLT. Additional patients will be enrolled to replace patients who are not considered DLT evaluable.

4.3.2. PK analysis sets

The PK concentration analysis sets (one unique set for each study drug used in the combination treatment) are subsets of the safety analysis set including patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for avelumab or talazoparib.

The PK parameter analysis sets (one unique set for each study drug used in the combination treatment) are the same as the concentration analysis sets, since the 2 reported PK parameters (C_{tough} and C_{max}) are observational: i.e. taken directly from concentration data.

4.3.3. Biomarker analysis set

The biomarker analysis set is a subset of the safety analysis set including patients who have at least one baseline biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

4.3.4. Immunogenicity analysis set

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

Phase 1b

There is no formal hypothesis testing in this phase. Due to the dynamic nature of the Bayesian allocation procedure, the exact sample size of the "Up-and-Down" matrix design using the mTPI approach cannot be determined in advance. It is expected that 12-36 patients will need to be enrolled in Phase 1b using the mTPI design (see Section 5.1.2).

Phase 2

In Phase 2, enrollment in each treatment group will be up to approximately 20 or up to approximately 40 patients in each treatment group (not including patients enrolled in Phase 1b) as shown in Figure 1.

With 20 patients in a treatment group, ORR can be estimated with a maximum standard error of 0.112. With 40 patients in a treatment group, ORR can be estimated with a maximum standard error of 0.079. Within each treatment group, ORR will be estimated and the 2-sided exact 90% confidence intervals (CIs) will be calculated. Table 4 provides the exact binomial 90% CI for ORR based on different observed responses in a treatment group.

Table 4. Sample Size and Exact 90% Confidence Intervals for ORR in each Treatment Group

N per treatment group	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%)
	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%)

CI=confidence interval; ORR=objective response rate

5.1.2. Decision rules

Phase 1b

Dose finding to identify a safe dose and RP2D of talazoparib to be used in combination with avelumab (all tumor types):

A safe dose will be determined using the adaptive mTPI design. The mTPI method relies upon a statistical probability algorithm, calculated using data from all patients treated in prior and current patient groups at the same dose level to determine whether future patient groups should involve dose re-escalation, no change in dose, or dose de-escalation. 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 (2013)[3], mTPI design is more efficient and safer than the 3+3 design. 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 Maximum Tolerated Dose (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 one 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. The underdosing interval corresponds to a dose re-escalation, overdosing corresponds to dose de-escalation, and proper dosing corresponds to staying at the current dose. 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 group 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 dose finding evaluation of the trial is completed when 12 DLT-evaluable patients have been treated at the highest dose levels associated with a DLT rate <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 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.

Phase 2

There are no formal decision rules in this phase of the study.

5.2. General Methods

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

- Dose level cohort D0 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 1 mg QD PO;
- Dose level cohort D-1 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 0.75 mg QD PO;
- Dose level cohort D-2 (Phase 1b): avelumab 800 mg IV Q2W plus talazoparib 0.5 mg QD PO;
- Cohort A1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with NSCLC;
- Cohort A2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with NSCLC and PD-1/L1 resistant and DDR Defect +;
- Cohort B1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with TNBC;
- Cohort B2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with HR+/HER2- breast cancer and DDR Defect + assay;
- Cohort C1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with recurrent platinum-sensitive ovarian cancer;
- Cohort C2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with recurrent platinum-sensitive ovarian cancer and BRCA defect;
- Cohort D (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with UC;
- Cohort E1 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with CRPC;
- Cohort E2 (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with CRPC and DDR defect+ assay;

- Cohort F (Phase 2): avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with advanced solid tumor with a germline or somatic BRCA1, BRCA2 or ATM gene defect.

Table 5 provides an overview of the summaries and the tabulations for this study.

Table 5. Study Summaries and Tabulations

Summaries	Analysis Population	Phase 1b	Phase 2	Phase 1b and Phase 2 combined
Baseline characteristics and disposition	FAS	- by treatment group - for all treatment groups combined	by treatment group	For all patients treated with talazoparib at RP2D
DLTs	DLT-evaluable set	- by treatment group - for all treatment groups combined	ND	ND
Efficacy data	FAS	- by treatment group - for all treatment groups combined	by treatment group	ND
Other safety data, exposure data, concomitant medications, non-drug treatment	Safety analysis set	- by treatment group - for all treatment groups combined	by treatment group	For all patients treated with talazoparib at RP2D
PK data for avelumab	PK analysis set	ND	ND	For all patients
PK data for talazoparib	PK analysis set	ND	ND	For all patients treated with talazoparib at RP2D
Biomarker data	Full analysis set	ND	by treatment group	ND
Immunogenicity data	Immunogenicity analysis set	- for all treatment groups combined	- for all treatment group combined	For all patients

ND = Not done

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The ‘center’ factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the ‘Follow-up Cancer Therapy’ eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using only data from the ‘Follow-up Cancer Therapy’ eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the first dose of study treatment amongst the following:

- Start date of anti-cancer drug therapy recorded in the ‘Follow-up Cancer Therapy’ eCRF pages

- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits (if such analyses are performed).

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dose of study treatment.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, stable disease (SD), non-CR/non-PD, or progressive disease (PD) can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as ‘ND’ or ‘NA’. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as ‘ND’ or ‘NA’.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to ‘All values reported as BLQ have been replaced with zero’ should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if fewer than 4 ($n < 4$) concentration values are available. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues the associated study drug.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if fewer than 4 ($n < 4$) concentration values are available. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level) in a given cycle, this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses for this cycle.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

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

5.3.3.1. Date of last contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

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

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact

- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.

- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b

6.1.1.1. Primary analysis

The following analyses will be based on the DLT-evaluable set for patients in the Phase 1b. DLTs will be listed and summarized by treatment group and for all treatment groups combined, including data from Phase 1b only (Table 5).

6.1.2. Objective response as assessed by the Investigator per RECIST v1.1

6.1.2.1. Primary analysis

The following analyses will be based on the FAS by treatment group using the data from Phase 2.

Treatment groups A1, A2, B1, B2, C1, C2, D and F (non-CRPC patients)

Assessment of response will be made using RECIST v1.1. Assessments below refer to investigator assessment.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the date of first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment group will also be calculated along with the 2-sided 90% CI using the Clopper-Pearson method [2] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option). Two-sided 95% CIs will also be calculated and reported.

In addition, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), PD, and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death

- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD too early' (ie, SD of insufficient duration).

Treatment groups E1, E2 and F (CRPC patients)

Assessment of response will be made using soft tissue assessment by RECIST v1.1 and bone lesion assessment by PCWG3. Assessments below refer to investigator assessment.

Best overall response (BOR) will be assessed based on reported overall soft tissue responses and PCWG3 bone scan assessment at different evaluation time points from the date of first dose of study treatment until documented disease progression, according to the following rules. Disease progression in bone disease must be confirmed at least 6 weeks later, as per PCWG3. Only assessments performed before the start of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

- CR = at least two determinations of CR in soft tissue per RECIST v1.1 at least 4 weeks apart and before first documentation of PD (in soft tissue per RECIST v1.1 or in bone by PCWG3).
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) in soft tissue per RECIST v1.1 at least 4 weeks apart and before first documentation of PD (in soft tissue per RECIST v1.1 or in bone by PCWG3), and not qualifying for a CR.
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the date of first dose of study treatment and before first documentation of PD (in soft tissue per RECIST v1.1 or in bone by PCWG3), and not qualifying for CR or PR.
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after date of first dose of study treatment and before first documentation of PD (in soft tissue per RECIST v1.1 or in bone by PCWG3), and not qualifying for CR or PR.
- PD = progression ≤ 12 weeks after date of first dose of study treatment (and not qualifying for CR, PR, SD or non-CR/non-PD).
- NE: all other cases.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have any on-treatment radiographic assessment of soft tissue and bone lesion due to early progression, who receive anti-tumor therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

ORR by treatment group (E1 and E2) will also be calculated along with the 2-sided 90% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option). Two-sided 95% CIs will also be calculated and reported.

In addition, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No evidence of disease at baseline
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the date of first dose of study treatment without further evaluable tumor assessments)
- PD too late (>12 weeks after the date of first dose of study treatment)

Special and rare cases where BOR is NE due to both early SD and late PD will be classified as ‘SD too early’ (ie, SD of insufficient duration).

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

The following analyses will be based on the FAS by treatment group in Phase 2 and separately by treatment group and for all treatment groups combined in Phase 1b (Table 5). Assessment of response will be made using RECIST v1.1 for treatment groups from Phase

1b (non-CRPC patients) and for treatment groups A1, A2, B1, B2, C1, C2, D and F (non-CRPC patients), and using RECIST v1.1 and PCWG3 for treatment groups from Phase 1b (CRPC patients) and for treatment groups E1, E2 and F (CRPC patients). Tumor-related endpoints will be analyzed based on investigator assessment.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameters of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Duration of response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

Phase 1b (non-CRPC patients) and Phase 2 treatment groups A1, A2, B1, B2, C1, C2, D and F (non-CRPC patients): The documentation of PD is as assessed by Investigator using RECIST v1.1.

If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 6.

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

Table 6. Outcome and Event Dates for DR Analyses for non-CRPC Patients

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

Phase 1b (CRPC patients) and Phase 2 treatment groups E1, E2 and F (CRPC patients): The documentation of PD is defined by either soft tissue progression as assessed by Investigator using RECIST v1.1 or by bone disease as assessed by Investigator using PCWG3.

If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 7.

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

Table 7. Outcome and Event Dates for DR Analyses for CRPC Patients

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD (if based on bone disease it should be the first documentation of bone disease PD that is subsequently confirmed [b]) or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment.

[b] For bone disease, PD must be subsequently confirmed to be counted as an event. The date of PD for bone disease is the date of first documentation of bone disease PD (that is subsequently confirmed)

Kaplan-Meier estimates[5] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 3, 6 and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

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

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 8 following the hierarchy shown.

Table 8. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

6.2.2.3. Time to response

Time to response (TTR) is defined, for patients with OR, as the time from the date of first dose of study treatment to the first documentation of objective response (CR or PR) which is subsequently confirmed.

Phase 1b (non-CRPC patients) and Phase 2 treatment groups A1, A2, B1, B2, C1, C2, D and F (non-CRPC patients): The first documentation of objective response (CR or PR) is as assessed by Investigator using RECIST v1.1.

Phase 1b (CRPC patients) and Phase 2 treatment groups E1, E2 and F (CRPC patients): The first documentation of objective response is the first objective evidence of soft tissue response as assessed by Investigator using RECIST v1.1 with no evidence of confirmed bone disease progression per PCWG3.

TTR (in months) = [first date of OR
– date of first dose of study treatment +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.4. Progression-free survival

Phase 1b (non-CRPC patients) and Phase 2 treatment groups A1, A2, B1, B2, C1, C2, D and F (non-CRPC patients)

Progression-Free Survival (PFS) is defined as the time from the date of first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment for patients who do not have an event (PD or death), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the date of first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 16 weeks after the date of first dose of study treatment) in which case the death will be considered an event.

In this study, antitumor activity will be assessed through radiological tumor assessments conducted at screening, every 8 weeks (± 7 days) for 1 year from start of study treatment, and then every 16 weeks (± 7 days) thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy.

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

PFS (months) = [date of event or censoring
– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates[5] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rates at 3, 6, 9, 12 and 15 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) [1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

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

Table 9. Outcome and Event Dates for PFS Analyses for non-CRPC Patiens

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of first dose of study treatment [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the date of first dose of study treatment	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after the date of first dose of study treatment the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment

Table 10. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/ date of first dose of study treatment	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

Phase 1b (CRPC patients) and Phase 2 treatment groups E1, E2 and F (CRPC patients)

Progression-Free Survival (PFS) is defined as the time from date of first dose of study treatment to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever occurs first.

The documentation of PD is defined by either soft tissue progression as assessed by Investigator using RECIST v1.1 or bone disease progression which is confirmed at least 6 weeks later as assessed by Investigator using PCWG3.

In this study, antitumor activity in patients with CRPC will be assessed through radiological tumor assessments conducted at screening, every 8 weeks (± 7 days) for 24 weeks from start of study treatment, and then every 12 weeks (± 7 days) thereafter until disease progression regardless of initiation of subsequent anti-cancer therapy.

The censoring and event date options to be considered for the PFS and DR analysis are presented in Table 11.

PFS (months) = [date of event or censoring
– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates[5] (product-limit estimates) will be presented by treatment group using the data from the Phase 2 together with a summary of associated statistics including the median PFS time with 2-sided 90% and 95% CIs. In particular, the PFS rate at 4, 6, 8, 10, 12, 14 and 18 months will be estimated with corresponding 2-sided 90% and 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option in

SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 11. Outcome and Event Dates for PFS Analyses for CRPC Patiens

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	Date of first dose of study treatment [a]	Censored [a]
PD (if based on bone disease, PD that is subsequently confirmed [b]) or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after date of first dose of study treatment	Date of PD (if based on bone disease it should be the first documentation of bone disease PD that is subsequently confirmed [b]) or death	Event
PD (if based on bone disease, PD that is subsequently confirmed [b]) or death after 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [c] documenting no PD [b] before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD (or for bone disease PD that is not subsequently confirmed [b]) and no death	Date of last adequate tumor assessment [c] documenting no PD [b] before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given (prior to PD for soft tissue disease or confirmed PD for bone disease [b])	Date of last adequate tumor assessment [c] documenting no PD [b] before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after date of first dose of study treatment the death is an event with date on death date

[b] For bone disease, PD must be subsequently confirmed to be counted as an event. The date of PD for bone disease is the date of first documentation of bone disease PD (that is subsequently confirmed)

[c] If there are no adequate post-baseline assessments prior to the PD or death, then the time without adequate assessment should be measured from the date of first dose of study treatment; if the criteria were met the censoring will be on the date of first dose of study treatment

Time of Follow-Up for PFS

A plot will be generated to compare planned and actual relative day of tumor assessments by treatment group. A Kaplan-Meier plot for PFS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the PFS censoring and event indicators. including the median time of follow-up for PFS with 2-sided 95% CIs.

6.2.2.5. Overall Survival

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

OS (months) = [date of death or censoring
– date of first dose of study treatment +1]/30.4375

Kaplan-Meier estimates[5] (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rates at 3, 6, 9, 12, 15, and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) [1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 12 following the hierarchy shown.

Table 12. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ date of first dose of study treatment OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 14 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

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

Time of Follow-Up for OS

A Kaplan-Meier plot for OS follow-up duration will also be generated to assess the follow-up time in the treatment groups reversing the OS censoring and event indicators, including the median time of follow-up for OS with 2-sided 95% CIs.

6.2.2.6. Time to PSA progression for patients with metastatic CRPC

The following analyses will be based on the FAS for each of the treatment groups E1 and E2.

Time to PSA progression for patients with metastatic CRPC is defined as the time from the date of first dose of study treatment 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. PSA progression must be confirmed by a second, consecutive PSA assessment ≥3 weeks later.

Time to PSA progression will be censored on the date of the last PSA assessment for patients who do not have an event (confirmed PSA progression), for patients who start a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing PSA assessments. Patients who do not have a baseline PSA assessment or who do not have a post-baseline PSA assessment will be censored on the date of first dose of study treatment.

PSA assessments will be conducted at screening, every 4 weeks ± 2 days and at EOT. The censoring and event date options to be considered for the time to PSA progression analysis are presented in Table 13.

Time to PSA progression (months)
= [date of PSA progression or censoring
– date of first dose of study treatment +1]/30.4375

Table 13. Outcome and Event Dates for Time to PSA progression analysis

Scenario	Date of event/censoring	Outcome
No PSA assessment at baseline	Date of first dose of study treatment	Censored
PSA progression (subsequently confirmed), after at most one missing PSA assessment.	Date of first PSA progression	Event
PSA progression (subsequently confirmed) after 2 or more missing PSA assessments	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
PSA progression not confirmed or no PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored
New anti-cancer therapy prior to confirmed PSA progression	Date of last PSA assessment documenting no PSA progression before new anti-cancer therapy is given or missed PSA assessments	Censored

Kaplan-Meier estimates[5] (product-limit estimates) will be presented by treatment group (E1 and E2) together with a summary of associated statistics including the median time to PSA progression with 2-sided 90% and 95% CIs. In particular, the PSA progression rate at 4, 6, 8, 10, 12, 14, and 18 months will be estimated with corresponding 2-sided 90% and 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (conftype=loglog default option

in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event and patients censored will be presented by treatment group. The time to PSA progression or censoring time will also be presented in a patient listing.

6.2.2.7. PSA response for patients with metastatic CRPC

The following analyses will be based on the FAS for each of the treatment groups E1 and E2.

PSA response is defined as PSA decline ≥50% compared to baseline. PSA response must be confirmed by a second, consecutive PSA assessment ≥ 3 weeks later.

PSA response will be assessed based on PSA assessments at different evaluation time points from the date of first dose of study treatment until PSA progression. Only PSA assessments performed before the start of any further anti-cancer therapies will be considered in the assessment of PSA response.

- PSA response = at least 2 assessments, at least 3 weeks apart with ≥ 50% reduction in PSA level from baseline.
- No PSA response = all other cases.

Each patient will have a PSA response status (0: no PSA response; 1: PSA response). PSA response rate is the proportion of patients with PSA response in the analysis set.

PSA response rate by treatment group (E1 and E2) will be calculated along with the 2-sided 90% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option). Two-sided 95% CIs will also be calculated and reported.

A spider plot of the percent change in PSA value from baseline per time point and a waterfall plot of the best percentage change in PSA value from baseline will be created. These plots will display for each patient with a baseline assessment and at least one post-baseline assessment.

6.2.2.8. CA-125 response for patients with ovarian cancer

The following analyses will be based on the FAS for each of the treatment groups C1 and C2.

CA-125 response is defined as ≥ 50% reduction in CA-125 levels from baseline. CA-125 response must be confirmed by a second, consecutive CA-125 value ≥ 4 weeks later.

CA-125 response will be assessed based on the CA-125 values (ng/mL) collected at baseline and at different time points from the date of first dose of study treatment until EOT, according to the following rule. Only CA-125 value collected before the start of any further anti-cancer therapies will be considered in the assessment of CA-125 response.

- CA-125 response = at least 2 consecutive assessments ≥4 weeks apart with ≥ 50% reduction in CA-125 level from baseline.

- No CA-125 response = all other cases

Each patient will have a CA-125 response status (0: no CA-125 response; 1: CA-125 response). CA-125 response rate is the proportion of patients with CA-125 response in the analysis set.

CA-125 response rate by treatment group (C1 and C2) will be calculated along with the 2-sided 90% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option). Two-sided 95% CIs will also be calculated and reported.

6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the concentration and PK analyses sets, which on this study are identical for each analyte, given that PK parameters are observational and correspond to the two PK samples, pre-dose/0H/Ctrough and post-dose/1H/EOI, as described in Section 3.2.3. Data for which time of collection cannot be confirmed will be excluded. Data will be summarized as shown in Table 5.

Concentrations for talazoparib and avelumab will be listed by study phase (Phase1b and Phase 2), treatment group, starting dose (talazoparib only), cycle, day and nominal collection time, and will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) as shown in Table 5.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean, and its associated %CV and 95% CI will be presented in tabular form for avelumab and talazoparib concentrations as shown in Table 5. Concentrations with zero/BLQ values will be excluded from the calculation of geometric means and their associated %CV. Data from patients who have undergone intrapatient dose reduction will be excluded from the summary statistics beginning at the time of the dose reduction .

- In order to assess the attainment of steady-state, C_{trough} and C_{max} for avelumab and predose and postdose concentrations for talazoparib will be plotted using box-whisker plots by cycle and day within cycle for the sub-sets of data corresponding to the summary statistics described above. Individual data points, the geometric mean and the median of the parameter in each treatment will be overlaid on the box plots. If a treatment group has limited evaluable PK data (n<4), matchstick plots showing changes in C_{trough} for each drug and C_{max} for avelumab in individual patients will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and/or pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab and talazoparib exposure and biomarkers or significant safety/efficacy endpoints.

Additional exploratory PK analyses may be performed through the study to assess the drug-drug interaction potential between avelumab and talazoparib exposures when administered in combination relative to when each agent is administered as monotherapy, and to monitor for consistency in each drug's exposure among the patient cohorts.

The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker endpoints

Secondary endpoints in the study are candidate predictive biomarkers in tumor tissue including PD-L1 expression, genomic scarring and mutations in genes associated with DDR at baseline.

Biomarker data will be analyzed based on the full analysis set. Data will be presented by treatment group including data from Phase 2 only.

Biomarkers values at screening will be listed and summarized.

Descriptive summary statistics (mean, SD, median, Q1, Q3, tertiles, coefficient of variation, minimum, and maximum) will be provided for each biomarker as follows:

- PD-L1 expression level as percentage of positive tumor cells, immune cells and tumor and immune cells combined in a sample
- Genomic scarring as measured by genomic loss of heterozygosity score
- Total number of DDR gene mutations
- Number of mutations present in each of the individual DDR genes

For PD-L1 expression level, patients may be classified as positive, negative, or some other category according to scoring algorithms and cut-offs established from external sources. If no external standards exist, patients may be stratified using the median, quartiles and tertiles. For example, NSCLC patients of treatment group A1 may be categorized based on PD-L1 expression level $\geq 50\%$, $< 50\%$ and >0, equal to 0 or Unknown. The number and percentage of patients by treatment group in each category will be tabulated.

For genomic scarring, as measured by genomic loss of heterozygosity score, for the total number of DDR gene mutations and for the number of mutations in DDR genes, patients may be classified as positive, negative, or some other category according to scoring algorithms and cut-offs established from external sources. If no external standards exist, patients may be stratified using the median, quartiles and tertiles. For example, patients will be classified as positive if they have a mutation in any one of the assessed DDR genes and will otherwise be classified as negative. The number and percentage of patients by treatment group in each category will be tabulated.

BOR will be summarized by treatment group and for each category following the methodology outlined in Section 6.1.2.1. The number of responders (patients with BOR of

CR or PR) will be tabulated relative to biomarker classifications using a contingency table and a Fisher's exact test will be performed.

DR, PFS and OS (if meaningful) will be summarized by treatment group and for each category following the methodology outlined in Sections 6.2.2.2, 6.2.2.4 and 6.2.2.5. The censoring rules for DR and PFS for treatment groups A1, A2, B1, B2, C1, C2, and D are as described in Table 6 and Table 9, and for treatment groups E1 and E2 are as described in Table 7 and Table 11.

6.2.6. Endpoints for immunogenicity data of avelumab and talazoparib

ADA and, if appropriate, nAb data for avelumab will be listed by study phase (1b or 2), treatment group and cycle. The percentage of patients with positive ADA and nAbswill be summarized separately for all patients in Phase 1b and for all patients in Phase 2, as well as combined across all available data from both study phases. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit.

Table 14. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative patients (titer < cutpoint)	Number of patients with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive patients (titer ≥ cutpoint)	Number of patients with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of patients with valid baseline ADA result
Treatment-boosted ADA	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab	Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response	If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response	If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable.

The effect of ADA on avelumab concentrations/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.

Blood samples for avelumab immunogenicity testing is collected pre-dose of Cycle 1 Day 1 and Day 15, and pre-dose in Day 1 of Cycles 2, 3, 4, 9, 12, 18, and 24. Samples collected pre-dose on the day of avelumab dosing will be included in the analysis.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb, if data permit.

Patients will be characterized into different ADA categories based on the criteria defined in Table 14.

The number and percentage of patients in each ADA and nAb category will be summarized, if data permit.

If data are analyzed for nAb, patients will be characterized into different nAb categories based on the criteria in Table 15. For nAb, treatment-boosted is not applicable since no titer result is available.

Table 15. Patients Characterized Based on Neutralizing Antibody Results (nAb Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
nAb never-positive	No positive nAb results at any time point	Number of patients with at least one valid ADA result at any time point
nAb ever-positive	At least one positive nAb result at any time point	Number of patients with at least one valid ADA result at any time point
Baseline nAb positive	A positive nAb result at baseline	Number of patients with valid baseline ADA result
Treatment-induced nAb	Patient is not nAb positive at baseline and has at least one positive post-baseline nAb result; or if patient does not have a baseline sample, the patient has at least one positive post-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)
Transient nAb response	If patients with treatment-induced nAb have (a single positive nAb result or duration between first and last positive result <16 weeks) and nAb result at the last assessment is not positive.	Number of patients with at least one ADA valid post-baseline result and without positive baseline nAb result (including missing, NR)
Persistent nAb response	If patients with treatment-induced nAb have duration between first and last positive nAb result ≥16 weeks or a positive nAb result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline nAb result (including missing, NR)

ADA = antidrug antibody, nAb = neutralizing antibody, NR = no result.

CCI [redacted]

[redacted] .

6.4. Subset Analyses

OR and DR (if meaningful) will also be summarized for patients in the following subsets including data from Phase 2.

Within each treatment group:

- ECOG: 0, ≥1
- Number of prior anti-cancer drug therapy regimens: 0, ≥1

NSCLC patients pooled from treatment groups A1 and A2:

- Histology: Non-squamous, Squamous
- Adenocarcinoma type: Yes, No
- Received prior platinum treatment for locally advanced or metastatic disease: Yes, No

Breast cancer (separately for treatment groups B1 and B2):

- Received prior platinum treatment for locally advanced or metastatic disease: Yes, No

Ovarian cancer patients in treatment group C1:

- BRCA status: BRCA defect, BRCA wild-type, Unknown

UC patients (treatment group D):

- Visceral disease: Yes, No
- Received prior platinum treatment for locally advanced or metastatic disease: Yes, No

CRPC patients pooled from treatment groups E1 and E2:

- Total Gleason score at diagnosis: ≤ 7, ≥ 8.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

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

6.5.1.1. Demographic characteristics

Demographic characteristics will be summarized using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not Reported
  - Ethnic origin: Hispanic/Latino (Yes/No/Not Reported)
  - Age (years): summary statistics
  - Age categories :
    - < 65 years, ≥ 65 years
    - < 65, 65-<75, 75-<85, ≥ 85 years
  - Pooled Geographical Region (as applicable):
    - North America
    - Europe
    - Asia
    - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall randomized population)
  - Geographic Region (as applicable):
    - North America
    - Latin America
    - Western Europe
    - Eastern Europe
    - Middle East
    - Australasia
    - Asia
    - Africa
  - Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis' and RECIST eCRF pages will be summarized for the following.

From the 'Primary Diagnosis' eCRF page:

- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to start date (months), defined as (start date – date of initial diagnosis)/30.4375

From the RECIST eCRF page:

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

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

6.5.1.4. Prior anti-cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer therapy
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic

Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.
The prior anti-cancer drugs will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer drug therapies will be included in the listing that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

6.5.2. Study conduct and patient disposition

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

6.5.2.1. Patient disposition

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

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated patients in each of the analysis sets defined in Section 4
- Number and percentage of patients with study drug ongoing (separately for each study drug administered in combination)
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation
- Number and percentage of patients who entered long-term follow-up
- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated patients by center

In addition, a cross tabulation of patients who have discontinued/are ongoing treatment with avelumab vs patients who have discontinued/are ongoing treatment with talazoparib will also be provided.

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of the study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn
- Patients who receive the wrong treatment or an incorrect dose
- Patients who receive an excluded concomitant medication
- Deviations from GCP.

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

The following analyses will be based on the safety analysis set by treatment group as shown in Table 5.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. I.e., cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit eCRF exposure page, if the patient received study treatment on that visit (i.e., any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (i.e., all study drugs had dose=0 at that visit). Use earliest start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;

- for the last cycle, actual cycle end date = actual cycle start date + 28 (in days) – 1 day

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized (per cycle and/or overall) as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The information that will be summarized depends on how the study drug is dosed (e.g., infusion cyclical, oral daily). The formulae below should be applied to each study drug separately even when study drugs are administered in combination.

The derivations below are provided assuming 1 cycle = 4 weeks and for the following study drugs (administered alone or in combination):

- Avelumab administered as a 1-hour IV infusion at a fixed dose of 800 mg once every 2 weeks in 4-week cycles.

- Talazoparib administered orally QD PO daily at dose of 1.0 mg, 0.75 mg or 0.5 mg.

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered (mg).

Intended duration of treatment with avelumab (weeks) =

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

where end date = start date of last cycle with non-zero dose of avelumab + 28 – 1

Duration of exposure to avelumab (weeks) =

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

Cumulative dose (mg) is the sum of the actual doses of avelumab received.

Actual Dose Intensity (DI)

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with avelumab (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/4-week cycle)
  = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle]

= [2 × 800 (mg)] / [1 (4-week cycle)]
= 1600 (mg/4-week cycle)

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [1600 (mg/4-week cycle)]

6.5.3.2. Exposure to Talazoparib

The dose level is calculated as actual dose administered (mg/day).

Intended duration of treatment with talazoparib (weeks) = (end date – date of first dose of talazoparib +1)/7,

where end date = date of last dose of talazoparib.

Duration of exposure to talazoparib (weeks) =

(last dose date of talazoparib – first dose date of talazoparib + 1)/7

Note: For talazoparib, the duration of exposure and the intended duration of treatment are the same.

Cumulative dose (mg) is the sum of the actual doses of talazoparib received in the study.

Actual Dose Intensity (DI)

- Overall actual DI (mg/week) = [overall cumulative dose (mg)] / [intended treatment duration (weeks)]

Relative Dose Intensity (RDI)

- RDI (%) = 100 × [overall cumulative dose] / [intended cumulative dose per week × number of weeks from first dose of talazoparib to last dose of talazoparib]

  = 100 × [overall cumulative dose] / [7 × d × duration of exposure to talazoparib in weeks]

where d=1.0, 0.75 or 0.5.

6.5.3.3. Dose reductions

Applicable to talazoparib. Dose reduction is defined as a change to a non-zero dose level lower than the RP2D.

The number and percentage of patients with at least one dose reduction as well as a breakdown of the number of dose reductions (1, 2, 3) will be summarized.

6.5.3.4. Dose interruptions

Applicable to talazoparib.

An interruption is defined a 0 mg dose administered on one or more days for talazoparib. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days, then it will be counted only once (example: If the actual dose on days 1-3 is at the RP2D and actual dose on days 4-5 is 0 mg, then the total number of dose interruptions is 1).
- If an interruption occurs for more than one day, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (example: If the actual dose on days 1, 3 and 5, is at the RP2D and actual dose on days 2 and 4 is 0 mg, the total number of dose interruptions is 2).

A dose interruption is not considered a dose reduction.

The number and percentage of patients with dose interruptions and the corresponding reasons will be summarized. A breakdown of the number of dose interruptions (1, 2, 3, ≥4) will be summarized.

6.5.3.5. Dose delays

Applicable to avelumab.

Dose Delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses.

For Cycle 1:

Dose Delay (days) = day of the first day of study drug -1

After the first dose of Cycle 1:

Dose Delay for Dose x (days)
= Date of Dose x – Date of Dose (x-1) – Planned days between two consecutive doses
= Date of dose x of study drug – Date of dose (x-1) of study drug – 15

Dose delays will be grouped into the following categories:

- No delay
- 1-2 days delay
- 3-6 days delay
- 7 or more days delay

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

No delay and 1-2 days delay will be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, i.e., the worst case of delay if patients have multiple dose delays will be summarized.

6.5.3.6. Infusion rate reductions

Applicable to avelumab.

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

6.5.3.7. Infusion interruptions

Applicable to avelumab.

An infusion interruption is defined as an infusion that is stopped and re-started on the same day (i.e., for a visit more than one infusion start time and infusion end time are recorded).

The number and percentage of patients with at least one infusion interruption as well as the frequency of patients with 1, 2, 3, or ≥4 infusion interruptions will be summarized.

6.5.4. Concomitant medications and non-drug treatments

The following analyses will be based on the safety analysis set by treatment group as shown in Table 5.

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

Concomitant medications will be summarized from the ‘General Concomitant Medications’ eCRF page.

Summary of concomitant medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under ‘Unavailable ATC classification’ category.

6.5.5. Subsequent anti-cancer therapies

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

Anti-cancer drug treatment will be provided in a data listing with data retrieved from 'Follow-up Cancer Therapy' eCRF page.

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

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations.

Summaries of AEs and other safety parameters will be based on the safety analysis set by treatment group as shown in Table 5.

Summaries described below by SOC and PT may further be presented by PT in decreasing frequency based on the frequencies observed in the overall group.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Dose Reduction:** adverse events leading to dose reduction of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Dose reduced).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).

- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan [SRP] and finalized for analysis of the current study data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current study data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency based on the frequencies observed for the group with all patients in the Phase 1b treated with talazoparib at the RP2D and in the Phase 2 combined.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to discontinuation of any study drug
  - TEAEs leading to discontinuation of all study drugs
  - Related TEAEs leading to discontinuation of any study drug
  - Related TEAEs leading to discontinuation of all study drugs

  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
  - irAEs
  - IRRs

- TEAEs by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to dose reduction

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to dose reduction of talazoparib by SOC, PT and treatment group.

6.6.1.3. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of any study drug by SOC and PT.
- Related TEAEs leading to discontinuation of any study drug by SOC and PT.

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

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression

- Study treatment toxicity
- AE not related to study treatment
- Unknown
- Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

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

- SAEs by SOC and PT
- Related SAEs by SOC and PT

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

6.6.4. Other significant adverse events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs, by treatment group:

- irAEs leading to death, by Cluster and PT
- irAEs, by Cluster and PT
- irAEs, Grade ≥ 3, by Cluster and PT
- Serious irAEs, by Cluster and PT.

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

The frequency (number and percentage) of patients with each of the following will be presented for IRRs, by treatment group:

- IRRs leading to death, by PT
- IRRs, by PT
- IRRs, Grade ≥ 3, by PT
- Serious IRRs, by PT.

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

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

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

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) × (Differential %value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq$ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count $\geq$ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) and with an ALP ≤ 2×ULN or missing will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The number and percentage of patients with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

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

- Serum Chemistry:

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

Parameters with NCI-CTC grades not available:

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

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

In this study, these apply to the following parameters:

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

6.6.5.2. Other laboratory parameters

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

- Coagulation: activated partial thromboplastin time (aPTT) and prothrombin time (INR).
- Urinalysis: all urinalysis parameters
- Other parameters: hormone, and immunology parameters
- Pregnancy test

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. A listing of CTCAE grading will also be generated for those laboratory tests.

6.6.6. Electrocardiogram

QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. If QTcB and QTcF methods do not adequately correct for HR and there are a sufficient number of patients (eg >30) with baseline ECGs, an alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on a linear regression method which yields, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b × RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT
- Corrected QT for heart rate will be computed as follows:

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

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

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

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

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

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5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53: 457-81, 1958.

9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the SRP for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 16. Unless otherwise noted, this case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

Table 16. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list, then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	Steps 3 and 4 will be checked concurrently. Step 5 will be checked if the criteria in Step 4 is met, irrespective of whether the Criteria in Step 3 is met.
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology) B) Histopathology / biopsy consistent with immune-mediated event Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	A) From the AE eCRF page. Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify. B) From the AE eCRF page. B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR, the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 17 and will be identified for IV drugs only.

Table 17. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs

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

Appendix 3. Abbreviations and Definitions of Terms

The following is a list of abbreviations that may be used in the Statistical Analysis Plan.

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATM	Ataxia-Telangiectasia Mutated
BOR	Best Overall Response
BRCA	BReast CAncer Gene
CA-125	Cancer Antigen 125
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{trough}	Lowest (trough) Concentration
CR	Complete Response
CRF	Case Report Form
CRPC	Castration Resistant Prostate Cancer
CSR	Clinical Study Report
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DDR	DNA Damage Repair
DLT	Dose-Limiting Toxicity
DR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
HER2	Human Epidermal Growth Factor Receptor 2
HR+	Hormone Receptor Positive
irAE	Immune-Related Adverse Event
IV	Intravenous
mCRPC	metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
nAb	Neutralizing Antibody
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease
PD-1	Programmed Death 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival

PR	Partial Response
PSA	Prostate-Specific Antigen
Q2W	Every 2 Weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
TBILI	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Maximum Plasma Concentration
TTR	Time-to-Tumor Response
UC	Urothelial Cancer
ULN	Upper Limit of Normal