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

## JAVELIN BRCA/ATM

## STATISTICAL ANALYSIS PLAN – B9991032

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| **Compounds:** | MSB0010718C<br>MDV3800, BMN 673 |
| **Compound Name:** | Avelumab<br>Talazoparib |
| **Version:** | 4.0 |
| **Date:** | 16-Dec-2021 |

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## APPENDICES

# 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991032 is based on the protocol amendment 1 dated 15NOV2018.

**Table 1. Summary of Major Changes in SAP Amendments**

| Version | Version Date | Summary of Changes |
|---|---|---|
| **4** | 16-Nov-2021 | The following changes were implemented:<br>• Section 2. "Introduction" – The definition of the primary analysis cutoff date was modified to allow longer patient follow-up.<br>• Section 6.2.5. "Biomarker endpoints" – Alternative categories for TMB were added grouping the categories medium and high. CCI [redacted]<br>• Section 6.4.1. "Objective response and progression-free survival" - Subset analyses by BRCA-dependent status and by BRCA-associated status were added.<br>• Section 6.6.1.1. "All adverse events" and 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.<br>• 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.<br>• 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.<br>• 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,<br>• Section 6.6.6. "Vital signs" - The vital sign summaries by visit were deleted. |
| 3 | 09-Sep-2020 | The following changes were implemented:<br>• 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.<br>• Section 4.3.2. "Biomarker analysis set" – the biomarker analysis set will include blood-based and tumor tissue-based biomarkers. |

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| | | • Section 6.2.2.2. “Duration of response” - the listing of duration of response time was deleted.<br>• Section 6.2.2.4. “Progression-free survival” - the summary of time of follow-up for PFS was simplified.<br>• Section 6.2.2.5. “Overall survival” - the summary of time of follow-up for OS was simplified.<br>• Section 6.2.2.7. “PSA response for patients with metastatic CRPC” – the plot of the change in PSA value from baseline was added.<br>• Section 6.2.2.10. “BICR vs Investigator Assessment” - the concordance analysis of BOR outcomes for investigator vs BICR was added.<br>• Section 6.4.1. “Objective response and progression-free survival” - subset analysis of duration of response were removed. The Kaplan-Meier plot for PFS by subset (if meaningful) and the subset analysis of patients with measurable disease at baseline based on BICR/investigator assessment were added.<br>• Section 6.5.1.3. “Disease characteristics” - the summary of substance use was deleted.<br>• 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 deleted.<br>• Section 6.5.1.4. “Prior anti-cancer therapies” – the summary of prior anti-cancer therapies by class was deleted.<br>• 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 deleted.<br>• Section 6.6.1.3. “Adverse events leading to interruption of study treatment” - the listing of all AEs leading to interruption of study treatment was added.<br>• 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.<br>• Section 6.6.5.2. “Other laboratory parameters” - the listing of laboratory results with CTCAE grading was added.<br>• Section 6.6.8. “ECOG performance status” - the ECOG shift table was deleted. |
| 2 | 04-Feb-2020 | The following changes in the SAP were implemented in accordance to protocol amendment 1.<br>C[redacted]<br>• Section 6.5.3.5. “Dose delays” - the window for dose delays was updated from 2 days to 3 days.<br>• Section 3.4.1. “Study drug, study treatment and baseline definitions” and Section 5.2. “General Methods” - the recommended Phase 2 dose (RP2D) for talazoparib when administered in combination with avelumab and the talazoparib starting dose for patients with moderate renal impairment were specified.<br>In addition, the following changes were implemented.<br>• Section 3.4.1. “Study drug, study treatment and baseline definitions” - removed definition of baseline for ECG assessments as no summaries will be provided (ECGs are only collected post-treatment if clinically indicated). |

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| | | • Section 3.5.1. and Section 6.6.1 “Adverse events” – updated definition of treatment-emergent adverse events to include only adverse events with onset dates during the on-treatment period.<br>• Section 5.3.1.1. “Pharmacokinetic concentrations” and 5.3.1.2. “Pharmacokinetic parameters” - summary statistics at a particular time point will not be presented if less than 3 evaluable measurements are available (whereas in V1 of the SAP this referred to more than 50% of the data missing).<br>• Section 6.1.1. “Objective response as assessed by the BICR per RECIST v1.1” – added "No evidence of disease at baseline" as a possible reason for best overall response of NE as applicable, for example, to patients with mCRPC with no measurable disease and no non-target lesions at baseline.<br>• 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.<br>• Section 6.2.3. “Pharmacokinetic endpoints” – removed requirements to present log-linear plots as only sparse samples are collected; clarified plots will display either mean or medians (but not both).<br>• Section 6.2.5. “Biomarker endpoints” - The category "unknown" for BRCA and ATM mutations was added. The number and percentage of patients will also be reported based on the full analysis set to include the patients in the category "unknown". The summaries for DR, PFS and OS for each biomarker category were removed.<br>• Section 6.2.6. “Endpoints for immunogenicity data of avelumab” –Kaplan-Meier estimates for ADA response time/duration of response, summary of ADA titers, and summaries of PK, safety and efficacy by immunogenicity status were removed – such analyses will be performed only if the study results warrant further exploration of these data.<br>• Section 6.4. “Subset Analyses” - subset analyses for efficacy endpoints will be performed only based on BICR assessment. Removed subset analyses for the following variables based on clinical importance, redundancy and/or number of patients expected in a subgroup: visceral disease, history of central nervous system, baseline lactate dehydrogenase, triple negative breast cancer, hormone receptor positive, total Gleason score at diagnosis, and all subset analyses for patients with pancreatic cancer.<br>• Section 6.5.1.3. “Disease characteristics” - The following disease characteristics will be summarized as categorical variables: tumor type, visceral disease, central nervous system metastasis, presence of liver metastasis in pancreatic cancer patients (all based on BICR assessment), baseline lactate dehydrogenase and the total Gleason score at diagnosis. Site of primary tumor will not be summarized as only collected in the eCRF for patients with UC. Time since initial diagnosis and time since diagnosis of local/regional recurrence of disease will not be summarized.<br>• Section 6.5.3. “Study treatment compliance and exposure” - removed by-cycle summaries.<br>• Section 6.5.3.4. “Dose interruptions” – the reason for dose interruption was removed from the analysis specifications.<br>• 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 related to avelumab and adverse events related to talazoparib (adverse events related |

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| | | to either study drug will continue to be summarized), adverse events excluding serious adverse events, adverse events leading both dose reduction and interruption of avelumab or talazoparib.<br>• Section 6.6.5 "Laboratory data" and subsections – descriptive summaries by visit were removed as data will be summarized based on worst CTCAE grade or based on laboratory abnormalities.<br>• Section 6.6.6. "Electrocardiogram" – removed the analyses of ECGs that are not applicable to this study as ECGs are only collected when clinically indicated.<br>• Section for "Physical Examination" was removed as data not collected in the eCRF.<br>• Appendix 1 "Immune-Related Adverse Events" - steps 3 and 4 of the algorithm will be checked concurrently.<br>Redundant listings or listings that do not provide meaningful information were removed. Minor editorial and consistency changes throughout the document. |
| 1 | 14-May-2018 | Not applicable (N/A) |

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991032. 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, pharmacokinetic [PK] data, immunogenicity data, biomarker data, and tumor assessment results by the Blinded Independent Central Review (BICR)). The primary analysis will include all data up to a cut-off date corresponding to at least 18 months after the last patient receives the first dose of study treatment. 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 Objective**

- To evaluate objective response rate (ORR) of avelumab in combination with talazoparib, in patients with locally advanced or metastatic solid tumors harboring BRCA1, BRCA2 or ATM defect.

**Secondary Objectives**

- To assess the overall safety and tolerability of avelumab in combination with talazoparib;
- To characterize the PK of avelumab and talazoparib when given in combination;
- To evaluate the immunogenicity of avelumab when given in combination with talazoparib;

- To assess other measures of the anti-tumor activity of avelumab in combination with talazoparib;
- To assess the correlation of anti-tumor activity of avelumab in combination with talazoparib with PD-L1 expression in baseline tumor tissue;
- To assess the correlation of anti-tumor activity and emergence of resistance with defects in a panel of key oncogenes, including BRCA1/2 and ATM, and tumor mutational burden (TMB) in circulating tumor DNA (ctDNA) and tumor tissue at baseline, during treatment and at the end of treatment.

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## 2.2. Study Design

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

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

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

# 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

## 3.1. Primary Endpoint

- Confirmed objective response (OR) in patients with locally advanced or metastatic solid tumors with BRCA 1/2 or ATM defect, as assessed by BICR, using RECIST v1.1 and, in patients with metastatic castration-resistant prostate cancer (mCRPC), RECIST v1.1 and PCWG3 (bone).

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 for patients with solid tumors except mCRPC and, according to RECIST v1.1 (soft tissue) and PCWG3 (bone) for patients with mCRPC, 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

- Adverse Events as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03), timing, seriousness, and relationship to study treatments;

  AEs will be graded by the investigator according to CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v4.03) and timing.

### 3.2.2. Efficacy endpoints

- Confirmed OR as assessed by the investigator, using RECIST v1.1 and, in patients with mCRPC, RECIST v1.1 and PCWG3;

- Time to event endpoints: Endpoints as assessed by BICR and as assessed by the investigator, using RECIST v1.1 and in patients with mCRPC, RECIST v1.1 and PCWG3, including time to tumor response (TTR), duration of response (DR), and progression-free survival (PFS). Additional time-to-event endpoints include overall survival (OS) for all patients and time to prostate-specific antigen (PSA) progression (≥25% increase) for patients with mCRPC;

  TTR is defined, for patients with an OR who have solid tumors except mCRPC, 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. TTR is defined, for patients with an OR who have mCRPC, as the time from the date of first dose of study treatment to the first documentation of soft tissue objective response (CR or PR) which is subsequently confirmed, with no evidence of confirmed bone disease progression on bone scan per PCWG3.

DR is defined, for patients with OR who have solid tumors except mCRPC, 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.

DR is defined, for patients with OR who have mCRPC, as the time from the first documentation of soft tissue objective response (CR or PR) per RECIST v1.1 and no evidence of confirmed bone disease progression by PCWG3 to the date of first documentation of PD by soft tissue evaluated per RECIST v1.1 or bone disease evaluated per PCWG3, or death due to any cause.

For patients with solid tumors except mCRPC, 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. For patients with mCRPC, PFS is defined as the time from the date of first dose of study treatment to the date of the first documentation of radiographic progression in soft tissue evaluated per RECIST v1.1, in bone evaluated per PCWG3, or death due to any cause, whichever occurs first.

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

Time to PSA progression for patients with mCRPC 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.

- PSA response ≥50% decrease and circulating tumor cells (CTC) count conversion for patients with mCRPC;

  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.

  CTC count conversion is defined as a decrease in CTC count from ≥ 5 CTC per 7.5 mL of blood at baseline to < 5 CTC per 7.5 mL of blood on study. CTC0, defined as a decrease in CTC count from ≥ 1 CTC per 7.5 mL to an undetectable level on study, will also be reported.

- Cancer antigen (CA)-125 response ≥50% decrease 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 including: pre-dose/trough concentrations ($C_{trough}$) for avelumab and talazoparib, 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 plasma concentration | Observed directly from data |
| $T_{max}$ [a] | Time for $C_{max}$ | Observed directly from data as time of first occurrence |
| $C_{trough}$ | Predose concentration during multiple dosing | Observed directly from data |

[a] For avelumab only

For avelumab, the actual time difference between avelumab end of infusion (EOI) captured in the eCRF and $T_{max}$ will also be reported.

For talazoparib, the post-dose concentration value and its actual time relative to talazoparib dose will be reported.

### 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.
- Presence of defects in a panel of key oncogenes, including BRCA 1/2 and ATM, and TMB in ctDNA and tumor tissue at baseline, during treatment, and at the end of treatment.

**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. |
| Presence of defects in a panel of key oncogenes from tumor tissue, from germline DNA and from ctDNA | Presence or absence of a deleterious or expected deleterious mutation in BRCA1, BRCA2 and ATM from tumor tissue (somatic defect), from germline DNA (germline defect), and from ctDNA. | Next generation sequencing followed by computational analysis. |
| Tumor mutational burden (TMB) from tumor tissue and from ctDNA | The total number of mutations in the tumor genome, or number of mutations per megabase of DNA if derived from targeted sequencing. | 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 or to talazoparib and '**study treatment**' (or '**treatment group**') refers to one of the following:

- Cohort 1: avelumab 800 mg IV Q2W plus talazoparib at the recommended Phase 2 dose (RP2D) in patients with locally advanced or metastatic solid tumors with one or more defects in the BRCA1 or BRCA2 genes;

- Cohort 2: avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with locally advanced or metastatic solid tumors with one or more defects in the ATM gene.

RP2D is the recommended Phase 2 dose for talazoparib when administered in combination with avelumab. RP2D for talazoparib was established at 1 mg PO QD. The starting dose of talazoparib for patients with moderate renal impairment (CLCR = 30-59 mL/min) will be 0.75 mg PO QD to account for the lower talazoparib clearance.

**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 immunogenicity analyses

The last available assessment prior to the start of treatment with avelumab is defined as 'baseline' result or 'baseline' assessment. If an assessment is planned to be performed prior to the first dose of avelumab in the protocol and the assessment is performed on the same day as the first dose of avelumab, it will be assumed that it was performed prior to avelumab administration, if assessment time point is not collected or is missing.

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 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.

### 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. PK analysis sets

The PK concentration analysis sets (one unique set for each study drug used in the combination treatment) are a subset of the safety analysis set and will include patients who have at least one concentration measurement for avelumab or talazoparib.

The PK parameter analysis sets (one unique set for each study drug used in the combination treatment) are a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for avelumab or talazoparib.

#### 4.3.2. 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.

### 4.3.3. 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 result for avelumab.

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## 5. GENERAL METHODOLOGY AND CONVENTIONS

### 5.1. Hypotheses and Decision Rules

#### 5.1.1. Hypotheses and sample size determination

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

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

- Cohort 1: if 66 responders (out of 150 patients, ORR of 44%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.841);
- Cohort 2: if 23 responders (out of 50 patients, ORR of 46%) are observed, the posterior probability of a true ORR ≥40% (considered a clinically relevant effect) will be ≥0.80 (0.807).

Table 4 provides the exact 95% confidence intervals (CIs) for ORR based on different observed number of responders in a given tumor type cohort.

**Table 4. Sample Size and Exact 95% Confidence Intervals for ORR**

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

CI=confidence interval; ORR=objective response rate.

### 5.1.2. Decision rules

An interim analysis will be performed to allow early termination of the cohorts for futility. Within each cohort, ORR based on confirmed PR or CR by BICR assessment will be estimated after at least 20 patients are treated and followed for 24 weeks, without holding patient enrollment in either cohort.

The decision rule is based on the observed ORR: if the probability of a true ORR ≥40% is ≤0.05 then the cohort will be stopped for futility. For example, if 4 or fewer responders are observed out of 20 patients treated in a cohort (ORR ≤20%) after the minimum follow-up specified above, then the cohort will be stopped for futility.

## 5.2. General Methods

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

- Cohort 1: avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with locally advanced or metastatic solid tumors with one or more defects in the BRCA1 or BRCA2 genes;
- Cohort 2: avelumab 800 mg IV Q2W plus talazoparib at the RP2D in patients with locally advanced or metastatic solid tumors with one or more defects in the ATM gene.

RP2D is the recommended Phase 2 dose for talazoparib when administered in combination with avelumab. RP2D for talazoparib was established at 1 mg PO QD. The starting dose of talazoparib for patients with moderate renal impairment (CLCR = 30-59 mL/min) will be 0.75 mg PO QD to account for the lower talazoparib clearance.

Baseline characteristics, disposition, efficacy data and PRO data will be summarized based on the FAS. Other data including safety data, exposure, and concomitant medications will be summarized based on the safety analysis set.

All analyses will be summarized separately by treatment group and for both treatment groups combined unless otherwise specified; some analyses will be summarized for the appropriate cohort only (eg: Cohort 1 for BRCA analyses, Cohort 2 for ATM analysis, see Section 6.2.5; Cohort 1 for QLQ-OV28, QLQ-PR25, and QLQ-BR23, see Section 6.3.2).

### 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 6.1.1 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 'On-Study Anti-Cancer 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', 'On-Study Anti-Cancer 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 generally 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 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, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.1.1). 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. If this is performed, a footnote or other documentation in the clinical study report (CSR) detailing the exclusions will be provided.

Summary statistics will not be presented at a particular time point if less than 3 evaluable measurements are available. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

#### 5.3.1.2. Pharmacokinetic parameters

Actual sampling time will be used for the derivation of PK 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.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if less than 3 evaluable measurements 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), this will be footnoted in summary tables or flagged in the listings and will not be included in the calculation of summary statistics or statistical analyses.

### 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 15$^{th}$ 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 1$^{st}$.
- 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 1$^{st}$.
- 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 (eg, 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 where “Subject Remains in Follow-up” or “Subject No Longer Being Followed for Survival” collected on the “Survival Follow-up” eCRF
- 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 or death).

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. If the imputation results in an end date prior to the imputed start date, then the imputed start date should be set to the end date.

- 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. Objective response as assessed by the BICR per RECIST v1.1

#### 6.1.1.1. Primary analysis

The following analyses will be based on the FAS by treatment group and for both treatment group combined. Assessment of response will be made using RECIST v1.1 for patients with solid tumors except mCRPC, and using RECIST v1.1 and PCWG3[5] for patients with mCRPC. Assessments below refer to BICR assessment. Similar analyses will be repeated using investigator assessment as secondary analysis.

**Patients with solid tumors except mCRPC**

**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). ORR is the proportion of patients with OR in the analysis set.

**Patients with mCRPC**

**Best overall response (BOR)** will be assessed based on reported overall soft tissue responses and bone scan assessment 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 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 in soft tissue per RECIST v1.1 at least 4 weeks apart and before first documentation of PD (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 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).
- 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 assessment of soft tissue or bone lesions 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). ORR is the proportion of patients with OR in the analysis set.

**ORR for all patients**

ORR by treatment group and for both treatment group combined will also be calculated along with the 2-sided 95% 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).

The posterior probability of ORR ≥40% using the observed number of responders (patients with BOR of CR or PR) and the non-informative prior of (0.5, 0.5) will be provided.

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 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 SD of insufficient duration 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 and for both treatment groups combined. Assessment of response will be made using RECIST v1.11 for patients with solid tumors except mCRPC, and using RECIST v1.1 and PCWG3 for patients with mCRPC. Tumor-related endpoints will be analyzed separately based on BICR assessments and 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.

**Patients with solid tumors except mCRPC**: The documentation of PD is 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

**Patients with mCRPC**: The documentation of PD is defined by either soft tissue progression using RECIST v1.1 or by bone disease using PCWG3, as described in Table 5.

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 as described for PFS in Table 6.

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

## Table 5. Criteria for Evidence of Radiographic Progression for Patients with mCRPC

| Date Progression Detected[a] | Criteria for Progression | Criteria to Confirm Progression | Criteria to Document Disease Progression on Confirmatory Scan |
|---|---|---|---|
| Week 8 | Bone lesions: 2 or more new lesions compared to the baseline bone scan by PCWG3 | Timing: At least 6 weeks after progression identified [b] | Persistence of at least 2 lesions seen at week 8 AND 2 or more new bone lesions on bone scan compared to week 8 scan |
| | Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1 | No confirmatory scan required for soft tissue disease progression | No confirmatory scan required for soft tissue disease progression |
| Week 16 or later | Bone lesions: 2 or more new lesions on bone scan compared to Week 8 bone scan | Timing: At least 6 weeks (or earlier, if no subsequent assessments performed) after progression identified [b] | Persistence of at least 2 of the lesions identified as new compared to week 8 |
| | Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1 | No confirmatory scan required for soft tissue disease progression | No confirmatory scan required for soft tissue disease progression |

[a] Progression detected by bone scan at an unscheduled visit during the flare window should follow the confirmation criteria outlined for week 8. Progression detected by bone scan at an unscheduled visit after the flare window should follow the confirmation criteria specified for week 16 or later.

[b] Confirmation must occur at the next available scan. When 3 or more successive unconfirmed PD events exist that are less than 6 weeks apart, but the 1st and 3rd unconfirmed PD events are ≥6 weeks apart, the 1st unconfirmed PD becomes the confirmed date of bone progression.

## Table 6. Outcome and Event Dates for DR Analyses

| Scenario | Date of event/censoring | Outcome |
|---|---|---|
| PD or death<br>- After at most one missing or inadequate post-baseline tumor assessment, OR<br>- ≤ 16 weeks after the date of first dose of study treatment | Date of PD or death | Event |
| PD or death<br>- 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 |
| New anti-cancer therapy given prior to PD or death | Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments | Censored |

| Scenario | Date of event/censoring | Outcome |
|---|---|---|

[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.

Kaplan-Meier estimates[4] (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 4, 6, 8, 10 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)[3] (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 7 following the hierarchy shown.

**Table 7. DR Censoring Reasons and Hierarchy**

| Hierarchy | Condition | Censoring Reason |
|---|---|---|
| 1 | Start of new anti-cancer therapy before event | 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] | Withdrawal of consent |
| 4 | No event and lost to follow-up in any disposition page | Lost to follow-up |
| 5 | 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.

**Patients with solid tumors except mCRPC**: The first documentation of objective response (CR or PR) is using RECIST v1.1.

**Patients with mCRPC**: The first documentation of objective response is the first objective evidence of soft tissue response using RECIST v1.1 with no evidence of confirmed bone disease progression per PCWG3.

TTR (in months) = [first date of OR – the 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

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.

**Patients with solid tumors except mCRPC**:

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 and every 8 weeks until PD regardless of initiation of subsequent anti-cancer therapy. After 52 weeks from the date of first dose of study treatment, tumor assessments will be conducted less frequently, ie, at 16-week intervals.

**Patients with mCRPC**:

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 as described in Table 8 or death due to any cause, whichever occurs first.

In this study, antitumor activity in patients with mCRPC will be assessed through radiological tumor assessments conducted at screening, every 8 weeks (± 7 days) until PD regardless of initiation of subsequent anti-cancer therapy. After 24 weeks from the date of first dose of study treatment, tumor assessments will be conducted less frequently, ie, at 12-week intervals.

The censoring and event date options to be considered for the PFS analysis are presented in Table 8.

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

**Table 8. Outcome and Event Dates for PFS Analyses**

| Scenario | Date of event/censoring | Outcome |
|---|---|---|
| No adequate baseline assessment | Date of first dose of study treatment [a] | Censored [a] |
| PD or death<br>- After at most one missing or inadequate post-baseline tumor assessment, OR<br>- ≤ 16 weeks after the date of first dose of study treatment | Date of PD or death | Event |
| PD or death<br>- 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 |
| New anti-cancer therapy given prior to PD or death | 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 and did not initiate new anti-cancer therapy, 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

Kaplan-Meier estimates[4] (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 4, 6, 8, 10, 12, 14, 16 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)[3] (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 9 following the hierarchy shown.

**Table 9. 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 before event | 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] | Withdrawal of consent |
| 5 | No event and lost to follow-up in any disposition page | Lost to follow-up |
| 6 | No event and [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.

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

**Time of Follow-Up for PFS**

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[4] (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 4, 6, 8, 10, 12, 14, 16, 18 and 24 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)[3] (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 10 following the hierarchy shown.

**Table 10. 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

Time to PSA progression for patients with mCRPC 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 the first dose of study treatment.

PSA assessments will be conducted at screening, every 4 weeks ± 2 days, and at the EOT. The censoring and event date options to be considered for the time to PSA progression analysis are presented in Table 11.

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

**Table 11. 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[4] (product-limit estimates) will be presented together with a summary of associated statistics including the median time to PSA progression with 2-sided 95% CIs. In particular, the PSA progression rate at 4, 6, 8, 10, 12, 14, 16, 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)[3] (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. 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

**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 on or 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 will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

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. CTC count conversion and CTC0 for patients with metastatic CRPC

The following analyses will be based on the FAS separately by treatment group and for both treatment groups combined.

**CTC count conversion** is defined as a decrease in CTC count from ≥ 5 CTC per 7.5 mL of blood at baseline to < 5 CTC per 7.5 mL of blood on study. Only the CTC count assessments performed on or before the start of any further anti-cancer therapies will be considered in the assessment of CTC count conversion. The analysis set will include all patients with CTC count ≥ 5 CTC per 7.5 mL at baseline. All other patients will be considered as non-evaluable. The patients in the analysis set will be counted as:

- CTC count conversion = one or more post-baseline assessment(s) of CTC count < 5 CTC per 7.5 mL
- No CTC count conversion = all other cases.

Patients with CTC count ≥ 5 CTC per 7.5 mL at baseline and who do not have a post-baseline CTC count assessment will be counted as no CTC count conversion. Each patient in the analysis set will have a CTC count conversion status (0: no CTC count conversion; 1: CTC count conversion). The CTC count conversion rate is the proportion of patients with CTC count conversion rate in the analysis set.

A waterfall plot of maximum percent decrease in CTC count from baseline will be created for all patients with CTC count ≥ 5 CTC per 7.5 mL at baseline. The plot will display the best percentage change from baseline in CTC count for each patient with a baseline assessment and at least one post-baseline assessment.

**CTC0** is defined as a decrease in CTC count from ≥ 1 CTC per 7.5 mL of blood at baseline to an undetectable level on study. Only the CTC count assessments performed on or before the start of any further anti-cancer therapies will be considered in the assessment of CTC0. The analysis set will include all patients with CTC count ≥ 1 CTC per 7.5 mL at baseline. All other patients will be considered as non-evaluable. The patients in the analysis set will be counted as:

- CTC0 = one or more post-baseline CTC count are at undetectable level(s)
- No CTC0 = all other cases.

Patients with CTC count ≥ 1 CTC per 7.5 mL at baseline and who do not have a post-baseline CTC count assessment will be counted as no CTC0. Each patient in the analysis set will have a CTC0 status (0: no CTC0; 1: CTC0). The CTC0 rate is the proportion of patients with CTC0 in the analysis set.

The CTC count conversion rate and CTC0 rate by treatment group and for both treatment groups combined will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

#### 6.2.2.9. 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.

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 on or 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 will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

A waterfall plot of maximum percent decrease in CA-125 value from baseline will be created. The plot will display the best percentage change from baseline in CA-125 value for each patient with a baseline assessment and at least one post-baseline assessment.

#### 6.2.2.10. BICR vs Investigator Assessment

Table 12. outlines the possible BOR outcomes by investigator and BICR.

**Table 12. Possible BOR Outcomes for Investigator vs BICR**

| BOR | | BICR Assessment | | | | | |
|---|---|---|---|---|---|---|---|
| | | **CR** | **PR** | **SD** | **Non-CR/ non-PD** | **PD** | **NE** |
| **Investigator Assessment** | **CR** | $n_{11}$ | $n_{12}$ | $n_{13}$ | $n_{14}$ | $n_{15}$ | $n_{16}$ |
| | **PR** | $n_{21}$ | $n_{22}$ | $n_{23}$ | $n_{24}$ | $n_{25}$ | $n_{26}$ |
| | **SD** | $n_{31}$ | $n_{32}$ | $n_{33}$ | $n_{34}$ | $n_{35}$ | $n_{36}$ |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Non-CR/ non-PD** | $n_{41}$ | $n_{42}$ | $n_{43}$ | $n_{44}$ | $n_{45}$ | $n_{46}$ |
| | **PD** | $n_{51}$ | $n_{52}$ | $n_{53}$ | $n_{54}$ | $n_{55}$ | $n_{56}$ |
| | **NE** | $n_{61}$ | $n_{62}$ | $n_{63}$ | $n_{64}$ | $n_{65}$ | $n_{66}$ |

$\sum_{i=1}^{6}(n_{ii})$ is the number of agreements on BOR between BICR and Investigator

$\sum_{i,j=1}^{6}(n_{ij})$ for i ≠ j is the number of disagreements on BOR between BICR and Investigator

N= $\sum_{i,j=1}^{6}(n_{ij})$

The following measures of concordance will be calculated for each treatment group:

- Concordance rate for BOR = $\sum_{i=1}^{6}(n_{ii})\ /N$
- Concordance rate for response = $[\sum_{i,j=1}^{2}(n_{ij}) + \sum_{i,j=3}^{6}(n_{ij})]/N$

Concordance rates are calculated for the treatment groups combined.

### 6.2.3. Pharmacokinetic endpoints

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group and for both treatment groups combined.

For this study, two PK samples (pre-dose and post-dose) are taken for each analyte in cycles with scheduled PK assessments.

For avelumab, the pre-dose and post-dose concentrations correspond to $C_{trough}$ and $C_{max}$ PK parameters, respectively. The actual time of the occurrence of avelumab $C_{max}$ will be reported as $T_{max}$. The time difference between avelumab EOI and $T_{max}$ will also be reported.

For talazoparib, the pre-dose and post-dose concentrations correspond to $C_{trough}$ PK parameter and the post-dose concentration, respectively. One table will be generated for the parameters, which will include concentrations labelled as “Pre-dose/$C_{trough}$” and “Post-dose”.

The post-dose talazoparib concentration and its actual time relative to talazoparib dose (ie, Actual Elapsed Time) will also be reported.

Pharmacokinetic parameters for avelumab and talazoparib will be taken from observed values or derived from plasma concentration-time data as described in Section 3.2.3.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV and 95% CI) of plasma concentrations and pharmacokinetic parameters will be presented in tabular form by cycle, day, and nominal time. Additionally, similar descriptive statistics will also be generated for dose-normalized avelumab and talazoparib pharmacokinetic parameters, as appropriate.
- Linear-linear plots of mean or median plasma concentrations by nominal time for avelumab and talazoparib will be presented for PK sampling days by cycle and study day.

- Pharmacokinetic parameters for avelumab and talazoparib will be listed and summarized by cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean, and its associated %CV, and 95% CI). For $T_{max}$, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV.
- The trough concentrations for avelumab and talazoparib will be plotted using a box whisker plot by cycle and day in order to assess the attainment of steady state. $C_{trough}$ (and $C_{max}$ as deemed appropriate) for avelumab and talazoparib will be plotted using box-whisker plots by treatment group and cycle and day within cycle for 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 $C_{trough}$ and/or $C_{max}$ or post-dose concentration for each analyte in individual patients will then be generated. The geometric mean of the parameter in each treatment will be overlaid in the plots. Patients who have undergone intra-patient dose reduction or escalation will be excluded from the summary tables and figures.
- Data from patients assigned a reduced talazoparib dose based on renal impairment status may be pooled with normal renal function patients receiving a 1 mg dose or may be presented separately at the discretion of the clinical pharmacologist.

### 6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between avelumab and/or talazoparib exposure and biomarkers or significant safety/efficacy endpoints. 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 and in ctDNA including, but not limited to, centrally assessed PD-L1 expression, BRCA1/2, ATM and TMB. Defects in a panel of key oncogenes, including BRCA1, BRCA2, and ATM will also be assessed in germline DNA.

Biomarker data will be analyzed based on the full analysis set or biomarker analysis sets, depending on the specific analysis, separately by treatment group and for both treatment groups combined, unless specified.

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, patients may be categorized based on PD-L1 expression level ≥ 50%, < 50% and >0, equal to 0, or Unknown. The number and percentage of patients in each category will be tabulated.

For TMB, patients will be classified as high, medium, low, or Unknown, or alternatively as high, low, or unknown. The number and percentage of patients in each category, by sample source (tumor tissue, ctDNA) and by timepoint (baseline, and when available on-treatment, and at the end of treatment), will be tabulated.

Where sample numbers of a given tumor histology are sufficient to support such an analysis, TMB and PD-L1 may also be analyzed as described above but tabulated based on individual tumor histologies.

For defects in BRCA1 and BRCA2 by central laboratory analysis, patients will be classified as positive, negative or unknown. The number and percentage of patients in each category of BRCA 1 defect, BRCA 2 defect, BRCA 1 or BRCA 2 defect, by sample source (somatic/tumor tissue, germline DNA, ctDNA), and by timepoint (baseline, and on-treatment/at the end of treatment as appropriate), will be presented for Cohort 1.

For defects in ATM by central laboratory analysis, patients will be classified as positive, negative or unknown. The number and percentage of patients in each category of ATM, by sample source (somatic/tumor tissue, germline DNA, ctDNA) and by timepoint (baseline, and on-treatment/at the end of treatment as appropriate) will be presented for Cohort 2.

The following analyses will be performed for each biomarker secondary endpoint.

BOR will be summarized for each category of the biomarkers following the methodology outlined in Section 6.1.1. 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.

CCI [redacted]

### 6.2.6. Endpoints for immunogenicity data of avelumab

All analyses described below are performed by treatment group and for both treatment groups combined.

Blood samples for avelumab immunogenicity testing will be collected pre-dose on Day 1 and Day 15 of Cycle 1, on Day 1 of Cycle 3 and then on Day 1 of Cycle 6, 12, 18, and 24. All samples should be drawn within 2 hours before start of avelumab infusion. Additional samples for anti-avelumab antibodies (and simultaneous PK draws for measurement of avelumab) will be collected at EOT visit.

Samples positive for ADA will be analyzed for titer and may be analyzed for nAb. Analyses of nAb data described in the following sections will only be conducted contingent upon assay and data availability at the time of reporting.

Patients will be characterized into different ADA categories based on the criteria defined in Table 13.

**Table 13. 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.

Patients will be characterized into different nAb categories based on the criteria in Table 14. For nAb, treatment-boosted is not applicable since no titer result is available.

**Table 14. 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 (including no positive ADA results at any time point and no nAb results) | 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 = not reportable.

The number and percentage of patients in each ADA and nAb category will be summarized.

In order to derive and interpret persistent and transient ADA responses, the ADA and nAb analyses described below will include patients with treatment-induced ADA or nAb, respectively.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND patient is ongoing treatment with avelumab, or
- the last ADA assessment is positive AND patient discontinued treatment with avelumab AND the last planned ADA assessment (EOT visit) is after the cut-off date. As data

permit, the analyses described above will be repeated for patients with treatment-induced nAb.

Time to nAb response and duration of nAb response are defined similarly based on first and last positive nAb result.

Based on the results observed, additional analyses may be performed for ADA including PK, safety and/or efficacy relationships.

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CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

## 6.4. Subset Analyses

### 6.4.1. Objective response and progression-free survival

OR and PFS (if meaningful) will also be summarized based on the FAS for patients in the following subsets and following the methodology outlined in Section 6.1.1 and in Section 6.2.2.4 based on BICR assessment.

The subset analyses will be presented for each cohort and subset, and for both cohorts combined and subset when appropriate. Subset analyses will be performed only if there are at least 10 patients in the associated cohort(s) and each subset. Subset analyses will be performed by tumor type. In addition, the following subset analyses will be performed.

For all patients and by tumor type:

- ECOG: 0, ≥1
- Number of prior anti-cancer drug therapy regimens: ≤ 2, ≥ 3
- PD-L1 status: Positive, Negative, Unknown
- TMB: High, Medium, Low, Unknown
- BRCA from local laboratory test: BRCA1, BRCA2, BRCA1 or BRCA2
- Measurable disease at baseline based on BICR assessment: Yes
- BRCA-dependent status: Yes, No
- BRCA-associated status: Yes, No

The definition of the BRCA-dependent status and BRCA-associated status of tumor types will be based on clinical assessment, using the BRCA result from the local laboratory test.

In addition, for patients with breast cancer:

- Received prior platinum treatment for locally advanced or metastatic disease: Yes, No
- Number of prior anti-cancer drug therapy regimens for locally advanced or metastatic disease: 0, 1, ≥ 2
- Received prior cytotoxic chemotherapy for locally advanced or metastatic disease: Yes, No

For patients with ovarian cancer:

- Number of prior platinum-based regimens: ≤ 2, ≥ 3
- Number of prior cytotoxic chemotherapy regimens: ≤ 2, ≥ 3
- Platinum status: sensitive, resistant

For patients with mCRPC:

- Measurable disease at baseline based on BICR assessment: Yes, No
- Measurable disease at baseline based on investigator assessment: Yes, No
- Received prior taxane-based regimen: Yes, No

### 6.4.2. PSA response for patients with metastatic CRPC

PSA response will be summarized based on the FAS for the subset of patients with mCRPC with measurable disease at baseline based on BICR assessment and the subset of patients with mCRPC and no measurable disease at baseline based on BICR assessment, following the methodology outlined in Section 6.2.2.7 and the definition in Section 6.5.1.3. The subset analyses will be presented for each cohort and subset, and for both cohorts combined and subset when appropriate.

### 6.4.3. CTC count conversion for patients with metastatic CRPC

CTC count conversion will be summarized based on the FAS for the subset of patients with mCRPC with measurable disease at baseline based on BICR assessment and the subset of patients with mCRPC and no measurable disease at baseline based on BICR assessment, following the methodology outlined in Section 6.2.2.8 and the definition in Section 6.5.1.3. The subset analyses will be presented for each cohort and subset, and for both cohorts combined and subset when appropriate.

## 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 by treatment group 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, Unknown
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - 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 treated 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 overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Tumor type, derived from the primary diagnosis eCRF page based on clinical assessment

From the RECIST eCRF page:

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

From the BICR assessment:

- Measurable disease (at least one target lesion in soft tissue by BICR assessment) at baseline (Yes, No, No disease)
- Involved tumor sites at baseline
- Visceral disease (yes, no)
- Central nervous system metastasis at baseline (yes, no)
- Presence of liver metastasis at baseline in pancreatic cancer patients (yes, no)

From the Gleason Score for Prostate Cancer:

- Total Gleason score at diagnosis ($\leq 7, \geq 8$)

From the Laboratory results:

- Baseline lactate dehydrogenase (LDH): <threshold, ≥ threshold (threshold value will come from external information; if it is not the case, the median value will be selected as threshold)

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, 0, 1, 2, 3, ≥4
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced – Metastatic/Local regional Disease-Recurrence
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

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

- At least one prior platinum-containing regimen
- Number of prior platinum-containing regimens: missing, 1, 2, 3, ≥4

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

- At least one prior platinum-containing regimen
- Number of prior platinum-containing regimens: missing, 1, 2, 3, ≥4

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

- At least one prior taxane-containing regimen
- Number of prior taxane-containing regimens: missing, 1, 2, 3, ≥4

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, country and 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
- 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 and for both treatment groups combined.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, 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 (ie, 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 (ie, all study drugs had dose=0 at that visit). Use 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 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 (eg, 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 dose of 800 mg once every 2 weeks in 4-week cycles.
- Talazoparib administered orally QD PO at the RP2D (mg) for talazoparib when administered in combination with avelumab.

#### 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 study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 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 is the RP2D (mg) for talazoparib when administered in combination with avelumab.

#### 6.5.3.3. Dose reductions

Applicable to avelumab. Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

Applicable to talazoparib. Dose reduction is defined as a change to a non-zero dose level lower than that planned in the protocol.

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, ≥4) 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, ie 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.

#### 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 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 – Date of dose (x-1) – 15

Dose delays will be grouped into the following categories:

- No delay
- 1-3 days delay
- 4-6 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 1-3 days delay will also be summarized together.

The number and percentage of patients with delayed study drug administration and maximum length of delay, ie, 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 (ie, 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.

**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.

### 6.6.1. 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 in what follows 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 treatment groups 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 PT as event category and MedDRA primary 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 by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to dose reduction of talazoparib
  - 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 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
- TEAEs leading to discontinuation of all study drugs by SOC and PT
- Related TEAEs leading to discontinuation of all study drugs 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 $\geq 3$, 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 v4.03. 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 v4.03 will be described using the worst grade. For those parameters which are graded with two toxicities, the toxicities will be summarized separately. Low direction toxicity grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, 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:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

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 ≥ 800/mm3

- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 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 a post-baseline TBILI ≥ 2×ULN, concomitantly with an ALT≥ 3×ULN or AST ≥ 3×ULN and with an ALP ≤ 2×ULN or missing will be provided.

**Parameters with NCI-CTCAE 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.

**Parameters with NCI-CTCAE 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

### 6.6.5.2. Other laboratory parameters

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 or with CTCAE grade ≥1 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

ECGs are collected only when clinically indicated. Patients with qualitative ECG abnormalities will be listed.

## 7. INTERIM ANALYSES

### 7.1. Introduction

An interim analysis will be performed to allow early termination of the cohorts for futility. Within each cohort, ORR based on confirmed PR or CR by BICR assessment will be estimated after at least 20 patients are treated and followed for 24 weeks, without holding patient enrollment in either cohort.

If based on the observed ORR, the probability of a true ORR ≥40% is ≤0.05 then the cohort will be stopped for futility. For example, if 4 or fewer responders are observed out of 20 patients treated in a cohort (ORR ≤20%) after the minimum follow-up specified above, then the cohort will be stopped for futility.

## 7.2. Interim Analyses and Summaries

At the interim analysis cutoff date in each cohort, OR analysis will be performed by the Sponsor. OR will be summarized by treatment group as described in Section 6.1.1.1. The interim analysis cutoff is defined as the date when at least 20 patients are treated and followed for 24 weeks. All tumor assessments available up to the analysis cutoff, including all patients in the FAS, will be included in the interim analysis.

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# 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 15. 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 15. 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.<br>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<br>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.<br>B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies"<br>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)<br><br>B) Histopathology / biopsy consistent with immune-mediated event<br><br>Event is in if<br>[Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)]<br>OR<br>[Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO]<br>OR<br>[Answer to 5B1 is NO AND answer to 5A is NO] | A) From the AE eCRF page.<br>Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No<br>If answer is Yes, check all that apply:<br>• Underlying malignancy / progressive disease.<br>• Other medical conditions.<br>• Prior or concomitant medications / procedures.<br>• Other. Specify.<br><br>B) From the AE eCRF page.<br>B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N<br>B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N<br>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 16 and will be identified for IV drugs only.

**Table 16. 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<br>• AE timing related to study drug ('DURING', 'AFTER') AND<br>• AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND<br>• 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<br>• 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 |
| AUC | Area Under the Curve |
| BICR | Blinded Independent Central Review |
| 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 |
| CSR | Clinical Study Report |
| CTC | Circulating Tumor Cell |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating Tumor DNA |
| CV | Coefficient of Variation |
| DDR | DNA Damage Repair |
| DOR | Duration of response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| CCI | [redacted] |
| EOT | End of Treatment |
| 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-L1 | Programmed Death-Ligand 1 |
| PFS | Progression-Free Survival |
| PR | Partial Response |

| | |
|---|---|
| CCI | [redacted] |
| 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 |
| ULN | Upper Limit of Normal |
| TMB | Tumor Mutational Burden |