Protocol C3441006

TALAPRO-1: A Phase 2, Open-Label, Response Rate Study of Talazoparib in Men With DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer Who Previously Received Taxane-Based Chemotherapy and Progressed on at Least 1 Novel Hormonal Agent (Enzalutamide and/or Abiraterone Acetate/Prednisone)

Statistical Analysis Plan (SAP)

Version: 3.0

Date: 01-Oct-2020

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3441006 is based on the Protocol Amendment #4 dated 15-November-2018.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1.0	Not Applicable	Not Applicable
2.0	1. Section 3.2 "Secondary Endpoint" - added a new secondary endpoint "Proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline" as defined in Protocol Amendment 4 2. Section 4.1 "DDR Deficient Measurable Disease Population" – the measurable disease was changed from being assessed by ICR to being assessed by investigator. 3. Section 4.3 "Other Analysis Set" – added "DDR Deficient population"; CTC evaluable population and PRO population were changed to be subset of DDR Deficient population. 4. Section 5.1 "Hypotheses and Decision Rules" – an interim analysis was added when 20 patients with BRCA1, BRCA2 or PALB2 mutations and measurable disease complete study treatment for at least 16 weeks or are otherwise no longer being followed; exact 2-sided 95% confidence intervals were provided. 5. Section 5.2.9 "Adequate Baseline" - extended the time required prior to date of first dose for adequate baseline assessment from 42 days to 49 days	The primary purpose of SAP revision is to align with Protocol Amendment 4 – addition of new secondary efficacy endpoint "Proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline". Additionally: • the DDR Deficient Measurable Disease population was modified from measurable disease based on ICR to measurable disease based on investigator assessment to align with a change in the ICR charter to remove the requirement for baseline reads prior to enrollment; • details were included to add an additional interim analysis to support the submission for breakthrough designation; • other changes were incorporated to provide clarification for programming and to align with the protocol specified assessment window.

	6. Section 6.1 "Primary Endpoint" - changed the time required after date of first dose from 8 weeks to 7 weeks when summarizing the reason of not evaluable 7. Section 6.2.4 "CTC Conversion and Null Rate" – added "Proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline" as a secondary endpoint and provided details on the assessment of this endpoint. 8. Section 6.5.2.3 "Tissue Sample Results for Enrollment" – provided details on analysis of tests and status for DDR deficiencies. 9. Section 7 "INTERIM ANALYSES" – clarified that the timepoints for interim analyses and final analysis 10. Minor editorial changes throughout the document	
3.0	1. Revised the SAP structure in Section 2.1, 3, and 4 to improve on flow, avoid repetition, and add consistency 2. Section 2.1, 5.1 and 7 – provided details on the final analysis 3. Section 4 – removed the DDR Deficient Population; renamed safety analysis set to safety population; and modified the definition of CTC Evaluable population and PK population 4. Section 5 – revised the definition of adequate post baseline tumor assessment; and added details of analyses to assess the impact of COVID-19 pandemic	The final analysis will occur when 100 DDR Deficient measurable disease patients have completed 6 month of study treatment or are otherwise no longer being followed. All efficacy analyses will be performed based on the DDR Deficient measurable disease population unless otherwise specified. Adverse Events of Special Interest (AESI) will include AML, MDS, Venous Thrombotic Events (VTE), pneumonitis, and second primary malignancies (other than hematologic).

	5. Section 6 – modified analysis population for efficacy endpoints; revised the censoring rule for duration of response; modified the subgroup analyses; added variables for baseline summaries; and changed the adverse events of special interest 6. Minor editorial changes throughout the document	

2. INTRODUCTION

This SAP provides detailed methodology for summary and statistical analyses of the data collected in study MDV3800-06 (C3441006), an international, phase 2, open-label, soft tissue response rate study of talazoparib in men with metastatic castration-resistant prostate cancer (mCRPC) with deoxyribonucleic acid (DNA) damage repair (DDR) deficiencies and previously treated with taxane-based chemotherapy and that progressed on at least 1 novel hormonal therapy (NHT; enzalutamide and/or abiraterone acetate/prednisone). 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. Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibition has been shown to produce clinical responses in mCRPC, particularly in patients with genomic defects in DNA repair genes. PARP inhibitors are thought to induce cell toxicity by inhibiting PARP catalytic activity as well as by trapping PARP-DNA complexes, which prevent DNA repair, replication, and transcription.

In this study approximately 100 men with progressive mCRPC with at least one genomic defect in a DNA repair gene likely to sensitize to PARP inhibition and measurable soft tissue disease per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be studied. The clinical benefit will be investigated with the primary efficacy endpoint of objective response rate (ORR).

Prior to protocol amendment 3, patients with either measurable or non-measurable disease were eligible for enrollment. Additionally, enrollment criteria included an expanded DNA repair gene panel. Patients without measurable disease and/or patients with mutations in the expanded DNA repair gene panel were subsequently excluded during protocol amendment 3; therefore, these patients will be excluded from primary efficacy analyses. Select efficacy and demography summaries and/or separate summaries or listing will provide efficacy and demography data on patients with mutations in the expanded DNA repair gene panel as well as on patients without measurable disease at baseline. Safety data from patients without measurable disease and/or patients with mutations in the expanded DNA repair gene panel will be included in safety summaries if the patient took

at least one dose of study treatment. All data from patients without measurable disease and/or patients with mutations in the expanded DNA repair gene panel will be provided in data listings.

The primary analysis will include all data up to a data cutoff date which will be determined when 100 patients complete at least 6 months of study treatment or are otherwise no longer being followed (eg withdrew consent, discontinued from the study, or died). All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

Interim analyses will be performed as described in Section 5.1. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date.

2.1. Study Objectives

Analysis	Objective
Primary Objective	
Efficacy	• To evaluate efficacy, of single agent talazoparib in DDR Deficient mCRPC as measured by ORR
Secondary Objective	
Efficacy	• To evaluate efficacy with respect to the following: • Time to objective response • Duration of response (DoR) • Proportion of patients with prostate-specific antigen (PSA) response ≥50% • Proportion of patients with conversion of circulating tumor cell (CTC) count • Time to PSA progression • Radiographic progression-free survival (PFS) • Overall survival (OS)
Safety	• To evaluate safety of talazoparib
PRO	• To evaluate the following patient-reported outcomes: • Time to deterioration in patient reported pain as assessed by the Brief Pain Inventory Short Form (BPI-SF) • Change from baseline in patient reported pain per BPI-SF • Change from baseline in patient reported outcome general health status as assessed by the European Quality of Life 5-Domain 5-Level Scale (EQ-5D-5L)
PK	• To evaluate the pharmacokinetics (PK) of Talazoparib
CCI [redacted]	
[redacted]	[redacted]

2.2. Study Design

This is an international, phase 2, open-label, soft tissue response rate study of talazoparib, a PARP inhibitor in development for treatment of men with DDR Deficient mCRPC.

In this study, approximately 100 men with progressive mCRPC and measurable soft tissue disease per RECIST 1.1 will be studied. Eligible patients must have previously received 1 to 2 chemotherapy regimens including at least 1 taxane-based regimen for treatment of metastatic prostate cancer, and progressed on at least 1 line of NHT for treatment of mCRPC.

Talazoparib capsules (1 mg/day) will be administered orally until: radiographic progression is determined by independent central review (ICR), unacceptable toxicity, patient withdraws consent, or death whichever occurs first. In addition, talazoparib can continue to be administered upon disease progression only if, in the opinion of the investigator the patient is clinically benefitting, no new concurrent systemic therapy is started, and the sponsor is notified. For patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30-59 mL/min/1.73 m^2) at screening, the starting dose will be 0.75 mg/day. Study treatment should not be discontinued based solely on PSA or CTC count increases.

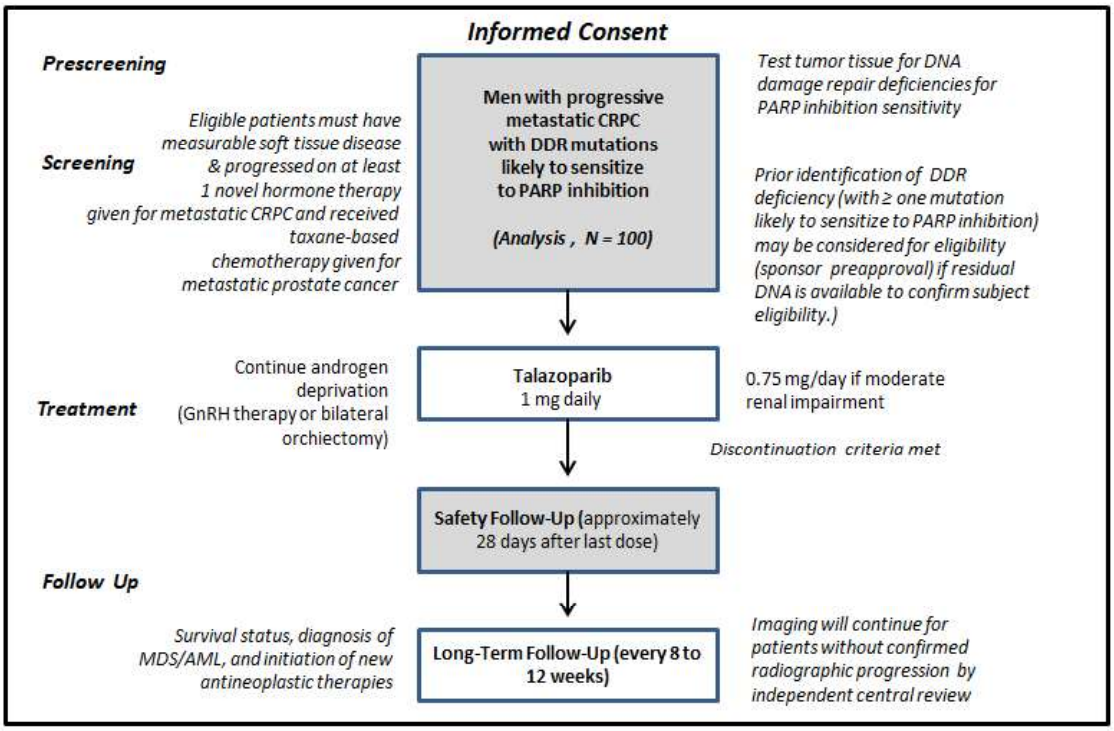
Study periods include prescreening (optional), screening, treatment, safety follow-up, and long-term follow-up. Safety follow-up after permanent discontinuation of study treatment will occur approximately 28 days after the last dose of study treatment or before initiation of a new antineoplastic or investigational therapy, whichever occurs first.

Radiographic assessments will be performed at screening, every 8 weeks through the first 24 weeks, then every 12 weeks thereafter. Scans may be obtained sooner than scheduled if disease progression is clinically suspected. Responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per Prostate Cancer Working Group 3 (PCWG3) criteria.

Long-term follow-up will occur every 8 to 12 weeks after safety follow-up. Radiographic imaging should continue during long-term follow-up for patients who discontinue study treatment for any reason other than radiographic progression determined by ICR, withdrawal of consent for follow-up, or death. Survival status and new antineoplastic (or anticancer) therapy will be assessed until the study is terminated. Diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) will continue per SAE reporting criteria. The study schematic is provided in Figure 1.

Note: The term antineoplastic therapy will be used interchangeable for anticancer therapy within this SAP.

Figure 1. Study Schematic



.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

Analysis	Endpoint	Additional notes
Efficacy	**Objective Response Rate (ORR):** defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses will be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review.	See Section 6.1

3.2. Secondary Endpoints

Analysis	Endpoint	Additional notes
Efficacy	**Time to objective response:** defined for patients with a confirmed objective soft tissue response, as the time from the date of first dose of study treatment to the first documented objective evidence of soft tissue response (CR or PR whichever is earlier) per RECIST 1.1 with no evidence of confirmed bone disease progression on bone scan per PCWG3, as assessed by the ICR. The response must be confirmed at least 4 weeks later as described in the primary endpoint.	See Section 6.2.1
	Duration of response (DoR): defined for patients with a confirmed objective soft tissue response, as the time from the first objective evidence of soft tissue response (CR or PR, whichever is earlier) per RECIST 1.1	See Section 6.2.2

	and no evidence of confirmed bone disease progression per PCWG3 to the date of first objective evidence of radiographic progression or death due to any cause without evidence of radiographic progression, whichever occurs first, as assessed by the ICR. Radiographic progression is defined as soft tissue progression per RECIST 1.1 or bone disease progression per PCWG3 by ICR.	
	Proportion of patients with PSA response ≥ 50%: defined as patients who have a ≥ 50% decrease in PSA levels (ng/mL) as measured by central laboratory.	See Section 6.2.3
	Proportion of patients with conversion of CTC count: defined as the proportion of patients with a CTC count ≥ 5 CTC per 7.5 mL of blood at baseline that decreases to < 5 CTC per 7.5 mL of blood any time on study. **Proportion of patients with a null CTC count:** defined as the proportion of patients with CTC count ≥1 per 7.5 mL of blood at baseline that decreases to CTC = 0 per 7.5 mL of blood any time on study. **Proportion of patients with baseline CTC count < 5 who showed increased CTC counts post-baseline:** defined as the proportion of patients with CTC count < 5 per 7.5 mL of blood at baseline that showed an increased CTC count, compared to baseline, any time on study.	See Section 6.2.4
	Time to PSA progression: defined as the time from date of first dose of study treatment to the date of PSA progression.	See Section 6.2.5
	Radiographic PFS: defined as the time from date of first dose of study treatment to the date of the first documented radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone per PCWG3 by ICR or death due to any cause without evidence of radiographic progression, whichever occurs first.	See Section 6.2.6
	Overall Survival (OS): defined as the time from the date of first dose of study treatment to death due to any cause.	See Section 6.2.7
Safety	**Safety of Talazoparib:** Assessment of safety will include AEs, incidence of dose modifications and of permanent treatment discontinuation due to adverse events, vital signs, and clinical laboratory tests.	See Section 6.6
PRO	• **Time to deterioration in patient reported pain as assessed by BPI-SF:** defined as the time from the date of first dose of study treatment to onset of pain progression, where pain progression is defined as a 2-point or more increase from baseline in the score of BPI-SF question 3: "Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours." • **Change from baseline in patient reported pain per BPI-SF** • **Change from baseline in patient reported outcome general health status as assessed by EQ-5D-5L.**	See Section 6.2.8
PK	• **Pre-dose trough and post-dose plasma concentrations for Talazoparib**	See Section 6.2.9

CCI [redacted]

[redacted]	[redacted]	[redacted]

CCI	[redacted]	[redacted]

3.4. Baseline Variables

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of talazoparib. The date of last dose of study treatment is the latest date of non-zero dosing of talazoparib.

No windowing will be applied when defining baseline.

For efficacy analyses and baseline characteristics associated with tumor assessments, the last assessment prior to the first dose of study treatment will serve as the baseline assessment.

For safety (including Eastern Cooperative Oncology Group [ECOG] performance status) and PRO endpoints, the last assessment performed on or prior to date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

3.5. Safety Endpoints

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

On-treatment is defined as the period between the first dose of the study treatment to 28 days after the last dose of study treatment, or before new systemic (ie not including surgery or radiotherapy) antineoplastic or investigational therapy, whichever occurs first.

Adverse events (AEs) will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study treatment will be considered as baseline assessments (see Section 3.4 for the definition of baseline).

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

An AE is considered treatment emergent if the event occurs during the on-treatment period.

Adverse Events of Special Interest (AESI) include AML, MDS, Venous Thrombotic Events (VTE), pneumonitis, and second primary malignancies (other than hematologic). These events will be defined based on a list of MedDRA PT specified prior to database release. A final list will be provided to programming prior to database release.

Hematology and chemistry result will be programmatically graded according to the NCI CTCAE version 4.03 for relevant parameters. A shift summary of baseline grade by maximum post-baseline grade will be presented. Parameters which cannot be graded will be summarized relative to the normal range (ie normal range high or normal range low). Additional details are provided in Section 6.6.3.

4. ANALYSIS SETS

Analysis Set	Population	Applicable Analysis (for additional information see Section 6)
DDR Deficient Measurable Disease Population	• All enrolled patients who have measurable soft tissue disease at screening by investigator assessment, have DDR deficiencies likely to sensitize to PARP inhibitor therapy and receive at least one dose of talazoparib.	• **Select baseline characteristics summaries** • **Primary and secondary efficacy analyses:** ORR, Time to objective response, DoR, PSA response, time to PSA progression, PFS, OS
Safety Population	• All patients who receive at least one dose of talazoparib including patients enrolled prior to amendment 3 with non-measurable disease and/or with DDR deficiencies which will likely or may sensitize the tumor to PARP inhibition as assessed using an expanded DDR gene panel.	• **Select baseline characteristics summaries** • **Safety analyses**
PK Population	• All patients from the safety population who have at least 1 reportable drug concentration data point.	• **PK analyses**
CTC Evaluable Population	• All patients with a baseline CTC assessment and at least 1 post-baseline CTC assessment from the DDR Deficient Measurable Disease population.	• **CTC analyses**
PRO Population	• all patients from the DDR Deficient Measurable Disease population with a baseline PRO assessment and at least 1 post-baseline PRO assessment prior to the end of treatment.	• **PRO analyses**

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary purpose of this study is to assess the ORR.

The study is designed to have an initial analysis after the first 20 DDR Deficient measurable disease patients receive study treatment for at least 8 weeks, a subsequent interim analysis when 60 DDR Deficient measurable disease patients complete at least 6 months of study treatment or are otherwise no longer being followed (ie have, withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up) and a final analysis. The final analysis will occur when 100 DDR Deficient measurable disease patients have completed 6 month of study treatment or are otherwise no longer being followed (ie have withdrawn consent, discontinue from the study, died, or are otherwise lost to follow-up).

Following the initial analysis after the 20 DDR Deficient measurable disease patients received study treatment for at least 8 weeks, it was of interest to further evaluate data from patients with a subset of DDR deficiencies. Therefore, an additional analysis has been added to review data after 20 patients with BRCA1, BRCA2 or PALB2 mutations and measurable disease receive study treatment for at least 16 weeks or are otherwise no longer being followed (ie have, withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

Table 2 provides the exact 2-sided 95% confidence interval (CI) under different scenarios at the time of the 60-patient interim analysis as well as the time of the final analysis. With 60 patients, the ORR can be estimated with a maximum standard error of 6.6%. With a total of 100 patients the maximum standard error is 5.1%. A sample size of approximately 100 patients is sufficient to demonstrate that if the observed best ORR is ≥23%, with the lower bound of the corresponding exact 2-sided 95% CI excluding 15.2%. Likewise, for the interim analysis of 60 patients, if the observed best ORR is ≥23%, the lower bound of the corresponding exact 2-sided 95% CI would exclude <13.4%. Additional scenarios are presented in Table 2.

Table 2. 95% CI for Different Scenarios

N=60 patients (interim)			N=100 patients (final)		
Responders	ORR point estimate	95% CI*	Responders	ORR point estimate	95% CI*
14	23.3%	(13.4%, 36%)	23	23%	(15.2%, 32.5%)
20	33.3%	(21.7%, 46.7%)	33	33%	(23.9%, 43.1%)
26	43.3%	(30.6%, 56.8%)	43	43%	(33.1%, 53.3%)
30	50%	(36.8%, 63.2%)	50	50%	(39.8%, 60.2%)

*Using the Clopper-Pearson method (Clopper, C. J.; Pearson, E. S. [1934])
CI = confidence interval; ORR = objective response rate

No formal stopping criteria are specified at the time of the interim analyses. Efficacy results may be discussed with regulatory authorities following the review after 20 patients with BRCA1, BRCA2 or PALB2 mutations and measurable disease per investigator and after the interim analysis at 60 patients with DDR Deficient and measurable disease per investigator. Additionally, as this is a single arm study with no formal hypothesis testing, no adjustments to the alpha level will be made in regard to the interim and final analyses for primary or secondary endpoints.

5.2. General Methods

Where applicable, 95% CI will be reported.

Patients with moderate renal impairment are eligible for enrollment and will receive a reduced starting dose of talazoparib. In all summary tables and analyses patients with and without moderate renal impairment will be combined regardless of starting dose, unless otherwise stated.

5.2.1. Pooling of Data by Center

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 subset analyses due to the high number of participating centers in contrast to the anticipated small number of patients treated at each center.

5.2.2. Nominal Timepoints

For all algorithms and analyses, visit labels as specified on the case report form (CRF) will be used as the nominal timepoint (ie assessment will not be slotted).

5.2.3. Definition of Study Day

There will be no study day 0. The study day for assessments occurring on or after the first dose of study treatment will be calculated as:

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

The study day for assessments occurring prior to the first dose of study treatment will be negative and calculated as:

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

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

5.2.4. Date of Last Contact

The date of last contact will be derived for patients not known to have died at the data cutoff date using the latest complete date (ie imputed dates will not be used in the derivation) among the following:

- All patient assessment dates (eg blood draws (laboratory, PK), vital signs, performance status, tumor assessments),
- Start and stop dates of concomitant therapies including non-drug treatments or procedures,
- Completion dates for PRO Questionnaires,
- Start and end dates of follow-up cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries,
- AE start and end dates,

- Last date of contact collected on the 'Survival Follow-up' CRF (do not use date of survival follow-up assessment unless status is 'alive'),
- Study treatment start and end dates, and
- Date of discontinuation on disposition CRF 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, or dates data were entered into the CRF, will not be used. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.5. Measurable Disease

A patient will be considered to have measurable disease if there is at least one target lesion identified at baseline meeting the following criteria:

- Non-lymph node lesions with longest diameter ≥10 mm when assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
- Lymph nodes with short axis ≥15 mm when assessed by CT or MRI.

5.2.6. DDR Deficient

A patient will be considered DDR Deficient if they have at least one of the following mutations by either central laboratory or based on historical results reported on the CRF:

- ATM
- ATR
- BRCA1
- BRCA2
- CHEK2
- FANCA
- MLH1
- MRE11A
- NBN
- PALB2 or
- RAD51C

5.2.7. Tumor Assessment Date

The date of soft tissue or bone assessment at each nominal timepoint as provided by ICR in the ICR data or by the investigator on the investigator overall objective tumor assessment (IOTA) CRF or the date of bone scan on the Bone Scan Assessment CRF will be utilized for the respective analyses.

5.2.8. Sum of Lesion Diameters

For lesions that are assessed as 'too small to measure', 5 mm will be imputed and used in the calculation of the sum of the lesion diameters.

5.2.9. Adequate Baseline

For efficacy analyses purposes, an adequate baseline for tumor assessments is defined using the following criteria:

- All tumor baseline assessments must be within 49 days (protocol specified window plus 7 days) prior to and including the date of first dose,
- All documented lesions must have non-missing assessments (ie non-missing measurements for target lesions and non-missing lesions status at baseline for non-target lesions), and
- A bone scan must have been performed to assess bone lesions.

5.2.10. Adequate Post Baseline Tumor Assessment

For purposes of censoring in applicable time to event analyses (eg radiographic PFS) an adequate assessment for patients with soft tissue disease at baseline is defined as an assessment where a response of CR, PR, Stable Disease (SD), non-CR/non-PD, or PD has been provided for soft tissue disease or patient has a bone assessment of confirmed PD (PDc) that has been performed within +/- 14 days of the soft tissue response assessment or where PD has been documented in either soft tissue or bone regardless of whether or not a complete assessment has been performed. For patients without soft tissue disease (ie only bone disease present at baseline) an assessment will be considered adequate assessment if a bone scan assessment has been performed. Timepoints where the response is not evaluable, or no assessment was performed will not be used for determining the censoring date. Adequate post baseline will be assessed separately for analyses based on ICR assessment and analyses based on investigator assessment.

5.2.11. Unscheduled Assessments

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety analyses. Additionally, unscheduled assessments will be used for efficacy analyses (eg defining date of progression/censoring, date of response, date of last contact).

5.2.12. Analyses for Binary Data

The rates of binary proportions will be presented along with a 2-sided exact 95% CI using the Clopper-Pearson method (Clopper, C. J.; Pearson, E. S. [1934]). This confidence interval is an exact interval, not relying on any normal approximations.

5.2.13. Analyses for Continuous Data

Descriptive statistics, including the number of non-missing observations, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous variables.

5.2.14. Analyses for Longitudinal Data

A longitudinal mixed effect model will be use for the analysis of data measured repeatedly over time. In fitting the model, time will be assumed to be a continuous variable and baseline will be used as a covariate. The analysis will be carried out using the method of restricted maximum likelihood and will assume an unstructured covariance matrix. The model estimated change from baseline values together with their 95% confidence intervals will be presented at specified post baseline visits.

5.2.15. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables. 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 with an assessment at that visit, unless otherwise specified.

5.2.16. Analyses for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of patients at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. The 95% confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of event at a particular timepoint will be generated using the log(-log) method with back transformation to a confidence interval on the untransformed scale. Summaries of the number and percentages of patients with an event will also be provided on summary tables and figures.

5.2.17. Analyses to Assess the Impact of COVID-19 Pandemic

The study enrollment may start during the COVID-19 pandemic period. If so, the following data summaries and analyses may be performed to assess the impact of COVID-19 on the trial population and study data. Additional analyses may be added in a SAP amendment if they are considered necessary to evaluate the outcome of the trial. Details of these summaries and analyses are included in the respective sections.

- Protocol deviations related to COVID-19
- COVID-19 related AEs and deaths
- Missing assessments due to COVID-19

5.2.18. COVID-19 Anchor Date

If additional analyses are needed to assess the impact of COVID-19 on the trial population and the study data, an anchor date will be used as a start date for COVID-19 pandemic related periods based on Pfizer guidance and standard operating procedure (SOP):

- For global pandemic reference date: Use the date the World Health Organization designated COVID-19 as a global pandemic - March 11, 2020

When producing data summaries intended to show the potential impacts of COVID-19 on the study, data will be presented as "before" and "during," where the anchor date is included in the "during" group.

A different anchor date may be used for purposes of regulatory submission should the regulatory authority requests.

5.3. Methods to Manage Missing Data

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

Any imputations will occur at the analysis dataset level and not the raw dataset level. Additionally, in all patient data listings imputed values will be presented and flagged as imputed.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' for not done, 'NR' for not reached or 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'. If too few events are observed in the KM analyses, then certain quartiles may not be estimable; hence NR should be presented.

5.3.1. Missing Dates

Date of Last Dose of Study Treatment

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

- If the last date of study treatment is completely missing and there is no End of Treatment (EOT) CRF page and no death date, the patient should be considered to be ongoing and the data cutoff date should be used as the last dosing date for the analysis; or

- If the last date of study treatment is partially missing and there is no EOT CRF page and no death date, then impute the last dose date as follows:

  = 31DECYYYY, if only Year is available and Year < Year of data cutoff date,

= Last day of the month, if both Year and Month are available and Year = Year of data cutoff date and Month < the month of data cutoff date, or

= data cutoff date, for all other cases; or

- If the last date of study treatment is completely or partially missing and there is EITHER an EOT CRF page OR a death date available (on or prior to the data cutoff date), then impute the last dose date as follows:

  = 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), or

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

Missing or Partial Death Dates

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

- If the entire date is missing it will be imputed as the day after the date of last contact (see derivation of date of last contact in Section 5.2.4); or

- If the day or 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, or

  - Missing day and month: January 1st of the year of death.

Date of Start of New Anticancer Therapy

Within this SAP the terms 'anti-cancer therapy' and 'antineoplastic therapy' are used interchangeable. Unless otherwise specified these refer to systemic therapy (ie not including radiotherapy or surgery) reported on the follow-up therapy CRF page.

Incomplete dates for new anti-cancer therapy will be imputed as follows and will be used to determine censoring dates for efficacy analyses:

- Date of progressive disease (PD) in the algorithm below references the earliest date of PD in soft tissue or confirmed PD in bone by investigator assessment.

- The end date of new anticancer therapy will be included in the imputation for start date of new anti-cancer therapy. If the end data of new anti-cancer therapy is:

  - completely missing then it will be ignored in the imputations below,

  - partially missing with only year available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy, or

  - 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 anticancer therapy.

- For patients who have not discontinued study treatment at the time of the data cutoff date, last dose of study treatment is set to the data cutoff date in the imputations below.

- If the start date of new anticancer therapy is completely or partially missing, then the imputed start date of new anticancer therapy is:

  - Start date of new anticancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

  - Only year (YYYY) for start of anticancer therapy is available

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

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

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

    THEN imputed start date = 01JANYYYY

  - Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available

    IF

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

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

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

THEN

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

ELSE IF

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

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

THEN

imputed start date = 01 MMM YYYY.

Other Missing Dates:

Imputations for other missing and partial dates including start and stop dates for adverse events and concomitant medications will follow the global Pfizer standard in place at the time of programming.

5.3.2. Missing Pharmacokinetic Data

Concentrations below the limit of quantification

For all calculations and figures, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. The BLQ values will be excluded from calculations of geometric means and their confidence intervals. 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. In listings BLQ values will be reported as below lower limit of quantification ("<LLOQ"), where LLOQ will be replaced with the corresponding value from the analytical assay used.

Deviations, Missing Concentrations and Anomalous Values

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

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

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

In summary tables of concentration-time profiles or PK parameters, statistics will be calculated by setting not calculated (NC) values to missing; and statistics will not be presented if more than 50% of the data are not collected, not calculated, or below LLOQ.

6. ANALYSES AND SUMMARIES

Throughout Sections 6.1 and 6.2, the term 'new anti-cancer treatment' is defined as:

- systemic anti-cancer (or antineoplastic) therapy, other than study treatment, or
- curative radiotherapy where the treatment intent is specified as 'primary treatment', or
- surgery where the treatment intent is specified as 'curative in intent' and the surgery outcome is either 'resected' or 'partially resected')

given after the first dose of study treatment.

6.1. Primary Endpoint

6.1.1. Objective Response Rate (ORR)

ORR will be summarized for the DDR Deficient Measurable Disease population. Measurable disease is defined in Section 5.2.5. ORR is defined as the proportion of patients with a best overall soft tissue response of CR or PR per RECIST 1.1 by independent central review. Soft tissue responses will be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no

evidence of confirmed bone disease progression on repeat bone scan at least 6 weeks later per PCWG3 criteria by independent central review. ORR will be summarized along with the 95% CI using the Clopper-Pearson method (Clopper-Pearson; 1934).

Additionally, the frequency (number and percentage) of patients with a best response of the following components will be tabulated:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD) or
- Not evaluable (NE)

Prior to determining the best overall soft tissue response, the date of confirmed bone progression (if applicable) will be determined. If confirmed bone progression is documented and the soft tissue response at the visit where the bone progression criteria were first met is not PD, the soft tissue timepoint response will be modified to PD prior to determining the best overall response (BOR). If there is a soft tissue disease assessment of CR, PR, SD, non-CR/non-PD or PD and a bone scan assessment was not performed, the BOR will be the same as has been provided for soft tissue disease. An example is provided in Table 3.

Table 3. Incorporation of Bone Progression into Best Overall Response

Example Number	Timepoint	Soft Tissue Response	Bone Assessment	Overall Soft Tissue Response Considering Bone Progression (derived)
1	Week 9	CR	Unconfirmed progression criteria met and subsequently confirmed (PD)	PD
	Week 17	CR	Progression criteria confirmed	PD
2	Week 9	CR	Unconfirmed progression criteria met and not confirmed (Non-PD)	CR
	Week 17	CR	Progression criteria NOT confirmed	CR
3	Week 9	SD	Non-PD	SD
	Week 17	PR	Unconfirmed progression criteria met and subsequently confirmed (PD)	PD
	Week 25	PR	Progression criteria confirmed	PD

CR = complete response; PD = progressive disease; PR = partial response

BOR will be assessed based on reported overall responses at different evaluation timepoints by the ICR or the investigator in respective analyses, after incorporating bone progression, from the date of first dose of study treatment until documented radiographical progression or start of new anti-cancer treatment (defined as systemic anti-cancer therapy [other than study treatment], or curative radiotherapy where the treatment intent is specified as 'primary treatment', or surgery where the treatment intent is specified as 'curative in intent' and the surgery outcome is either 'resected' or 'partially resected') given after the first dose of study treatment according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart and documented before progression (including progression in the bone) and start of new anti-cancer treatment,
- PR = at least two determinations of PR or better (and not qualifying for a CR) at least 4 weeks apart and before progression (including confirmed progression in the bone) and start of new anti-cancer treatment,
- SD (for patients with at least one measurable lesion at baseline) = at least one SD assessment (or better and not qualifying for CR or PR) ≥7 weeks after the date of first dose and before progression (including confirmed progression in the bone) and the start of new anti-cancer treatment,
- Non-CR/Non-PD (for patients with only non-target disease at baseline) = at least one Non-CR/Non-PD assessment (or better and not qualifying for CR or PR) ≥7 weeks after the date of first dose and before progression (including progression in the bone) and the start of new anti-cancer treatment,
- PD = progression ≤16 weeks after the date of first dose and not qualifying for CR, PR, SD, or Non-CR/Non-PD. Although response is being measured by RECIST in soft tissue disease, a patient will be considered to have PD if confirmed progression is noted in the bone per PCWG3,
- Not Evaluable (NE) = all other cases.

Clinical deterioration will not be considered as documented disease progression.

Patients with BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- Early death (defined as death prior to 8 weeks after the date of first dose),
- No post-baseline assessments, for reasons other than early death,
- All post-baseline assessments have overall response NE,
- New anti-cancer treatment started before first post-baseline assessment,

- SD of insufficient duration (<7 weeks after the date of first dose), or
- PD too late (>16 weeks after the date of first dose).

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

A listing of BOR for patients in the DDR Deficient Measurable Disease Population will be provided by mutation type.

Waterfall Plot

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 based on both the investigator and ICR assessment. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one valid post-baseline assessment. Only tumor assessments performed before the start of any further anti-cancer treatment and prior to documented progression in soft tissue or bone will be considered. Waterfall plots will include both patients with DDR deficiencies defined based on the genes noted in Section 5.2.6 as well as those with mutations from the expanded gene panel. Patients will be color coded based on mutation type.

6.1.2. Sensitivity Analysis

The ORR along with 95% CI and tabulations of the response components noted above will be provided using investigator assessments.

Concordance between ICR and Investigator assessment will be explored for the DDR Deficient Measurable Disease Population.

Table 4 outlines the possible BOR outcomes by ICR and investigator.

Table 4. Possible BOR Outcomes for ICR and Investigator

BOR		ICR 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}

BOR = best overall response; ICR = independent central review; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

$\Sigma^{6}_{i=1}(n_{ii})$ is the number of agreements on BOR between ICR and Investigator.

$\Sigma^{6}_{i,j=1}(n_{ij})$ for $i \neq j$ is the number of disagreements on BOR between ICR and Investigator

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

The following measures of concordance will be calculated:

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

6.2. Secondary Endpoint(s)

6.2.1. Time to Objective Response

Time to objective response is defined for patients from the DDR Deficient Measurable Disease population with a confirmed objective response of CR or PR per modified RECIST 1.1 without documentation of confirmed bone progression, as the time from date of first study dose of study treatment to the first documented objective evidence of soft tissue response (CR or PR) with no evidence of confirmed bone disease progression on bone scan per PCWG3. The response must be confirmed at least 4 weeks later as described in the primary endpoint. Analyses will be in months (date of first response– date of first dose of study treatment)/30.4375.

Descriptive statistics (mean, standard deviation, median, minimum, maximum, and quartiles) will be provided.

Analyses will be provided based on both the investigator and ICR assessment.

6.2.2. Duration of Response

Duration of response (DoR) is defined, for patients from the DDR Deficient Measurable Disease population with a confirmed best overall response of CR or PR per modified RECIST 1.1 without documentation of confirmed bone progression, as the time from first documentation of objective response (CR or PR) to the date of first objective evidence of soft tissue progression per modified RECIST 1.1 or confirmed bone disease progression per PCWG3 or death due to any cause without evidence of radiographic progression, whichever occurs first. The censoring rules for DoR are as described for radiographical PFS in Section 6.2.2; however, patients will not be censored for inadequate baseline assessment or for no adequate post-baseline assessment, as only patients with an objective response are included in this analysis of DoR.

DoR (months) = [date of event or censoring– first date of CR/PR +1]/30.4375.

If at least 10 subjects achieve a best ORR of CR or PR and subsequently have an event, Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary

of associated statistics including the median DoR with two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley. Otherwise only listings will be provided. Analyses will be provided based on both the investigator and ICR assessment.

A summary plot of time to response plus duration of response for each patient with a CR or PR will be provided for the DDR Deficient Measurable Disease population. Additionally, patients will be identified by mutation type and patients from the expanded gene panel who achieve a confirmed CR or PR will also be included.

6.2.3. PSA Response

PSA response is defined as a decline from baseline PSA (ng/mL) by at least 50%. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. Patients with a baseline PSA assessment and at least one post baseline PSA assessment and patients with a baseline PSA assessment will be analyzed for this endpoint separately. Only assessments performed from the date of first dose of study treatment until confirmed PSA progression or start of new anti-cancer treatment (defined as systemic anti-cancer therapy [other than study treatment], or curative radiotherapy where the treatment intent is specified as 'primary treatment', or surgery where the treatment intent is specified as 'curative in intent' and the surgery outcome is either 'resected' or 'partially resected'), given after the first dose of study treatment will be considered.

The proportion of patients in the DDR Deficient Measurable Disease population with confirmed PSA decline ≥50% compared to baseline will be calculated along with the 95% CI using the Clopper Pearson method (exact CI for a binomial proportion).

An additional analysis of the proportion of patients in the DDR Deficient Measurable Disease population with confirmed PSA decline ≥90% compared to baseline will be calculated along with the 95% CI using the Clopper Pearson method (exact CI for a binomial proportion). Patients with a baseline PSA assessment and at least one post baseline PSA assessment and patients with a baseline PSA assessment will be analyzed for this endpoint separately. Only assessments performed from the date of first dose of study treatment until confirmed PSA progression or start of new anti-cancer treatment (defined as systemic anti-cancer therapy [other than study treatment], or curative radiotherapy where the treatment intent is specified as 'primary treatment', or surgery where the treatment intent is specified as 'curative in intent' and the surgery outcome is either 'resected' or 'partially resected'), given after the first dose of study treatment will be considered.

PSA (ng/mL) values and change from baseline will also be summarized descriptively by visit. A waterfall plot of maximum percent reduction in PSA values will be provided for patients in the DDR Deficient Measurable Disease population.

6.2.4. CTC Conversion Rate

A summary of the median and range of baseline and maximum percent decrease from baseline in CTC counts will be provided for patients in the CTC evaluable population.

CTC count conversion rate is defined as any decline from 5 or more CTC per 7.5 mL at baseline to <5 CTC per 7.5 mL post baseline. Patients with a CTC count <5 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint. The proportion of patients with a conversion to <5 will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion).

The rate of null CTC count is defined as CTC=0 per 7.5 mL of blood at any time post baseline. Patients with a CTC count of 0 per 7.5 mL of blood at baseline are not analyzed for this conversion endpoint. The proportion of patients with a null CTC count will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion).

The proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline is defined as the proportion of patients with CTC count <5 per 7.5 mL of blood at baseline that showed any increase in CTC counts post-baseline. Patients with a CTC count ≥5 per 7.5 mL of blood at baseline are not analyzed for this endpoint. The proportion of patients with baseline CTC counts <5 who show increased CTC counts post-baseline will be calculated along with the two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion).

6.2.5. Time to PSA Progression

Time to PSA progression will be summarized using the Kaplan-Meier method as described in Section 5.2.16. The primary population for analysis will be the DDR Deficient Measurable Disease population.

Time to PSA progression is defined as the time from the date of first dose of study treatment to the date of PSA progression, which is subsequently confirmed. Patients without confirmed PSA progression will be censored at the date of the last PSA assessment. Patients without any post baseline assessments will be censored at date of first dose of study treatment.

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

For patients with PSA declines, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

For patients with no PSA declines, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the baseline is documented after 12 weeks of treatment, which is confirmed by a second consecutive value at least 3 weeks later.

Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median and quartiles with two-sided 95% CIs.

Frequency (number and percentage) of patients with an event or censoring will be presented.

6.2.6. Radiographic Progression-free Survival (PFS)

Radiographic PFS will be summarized using the Kaplan-Meier method as described in Section 5.2.16. The primary population for analysis will be the DDR Deficient Measurable Disease population.

Radiographic PFS is defined as the time from date of first dose of study treatment to first objective evidence of radiographic progression as assessed in soft tissue per modified RECIST 1.1 or confirmed progression in bone per PCWG3 guidelines by ICR or death without documented radiographic progression, whichever occurs first, and will be summarized in months using the following calculation:

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

The documentation required for the determination of radiographic progression is shown in Table 5.

Table 5. Criteria for Evidence of Radiographic Progression

Date Progression Detected (Visit)[1]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at week 17 visit[2]	Persistence of at least two of the lesions seen at week 9 AND 2 or more additional new bone lesions on bone scan compared to week 9 scan (2+2 rule). Date of progression is the date of the first post treatment scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 17 or later	Bone lesions: 2 or more new lesions on bone scan compared to week 9 bone scan	Timing: at least 6 weeks after progression identified or at next imaging timepoint[2]	At least 2 of the lesions first identified as new compared to week 9 must be still present. Date of progression is the date of the scan that first documented 2 or more new lesions.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression

1. Progression detected by bone scan at an unscheduled visit either before week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
2. 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.

CT = computed tomography; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

For purposes of censoring for PFS, new anti-cancer treatment includes any systemic anti-cancer therapy (other than study treatment), curative radiotherapy where the treatment intent is specified as 'primary treatment', or surgery where the treatment intent is specified as 'curative in intent' and the surgery outcome is either 'resected' or 'partially resected given after the first dose of study treatment. Patient receiving palliative radiotherapy or other surgeries such as biopsies before documented radiographic progression will not be censored.

PFS data will be censored as follows, where two or more missed assessments is defined as more than 175 days since the last adequate assessment (two 12-week assessments including a 7-day assessment window):

Table 6. PFS Event/Censoring Rules

Event/Censoring Categories	Date of Event/Censoring
Patients who did not have radiographic progression at any time and did not die.	Censor on the date of the last adequate tumor assessment (see Section 5.2.7) on or before the data cutoff date
Patients who started a new anti-cancer treatment prior to radiographic progression or death (where death has occurred without radiographic progression).	Censored on the date of last adequate tumor assessment prior to the start of new anti-cancer therapy (note if the date of progression occurs on the same date as the start of new antineoplastic therapy, the progression will be counted as an event).
Patients who did not have an adequate baseline or who do not have any post baseline tumor assessments and did not die within 175 days after first dose of study treatment	Censor on the date of first dose of study treatment.
Patients who had 2 or more missed scheduled tumor assessments (defined as 175 days or more between the last adequate assessment and the event date) immediately prior to radiographic progression or death	Censor on the date of the last adequate tumor assessment without evidence of disease progression before the 2 missed assessments.
Patients who did not have baseline or post baseline tumor assessments but died within 175 days after the date of the first dose of study treatment	Event of progression is established on the date of death.
Patients with radiographic progression prior to the start of new anti-cancer treatment and not after 2 or more consecutive missed assessments (defined as 175 days or more between the last adequate assessment and the event date)	Event of progression is established on the date of progression.
Patient without radiographic progression and who died prior to the start of new anti-cancer therapy and not after 2 or more consecutive missed assessments (defined as 175 days or more between the last adequate assessment and the event date)	Event of progression is established on the date of death.

PFS = progression free survival

If a patient meets the criteria for more than 1 censoring rule, the data will be censored with the earliest censoring date.

Kaplan-Meier estimates will be presented together with a summary of associated statistics including median PFS and rates at 3, 6, 9, and 12 months with two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at months 3, 6, 9, and 12 will be derived using the log(-log) method.

Frequency (number and percentage) of patients with each event type (progression or death) and censoring reasons will be presented along with the overall event and censor rates.

Reasons for censoring will be summarized according to the categories in Table 7. If a patient meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 7. Censoring Reasons and Hierarchy for PFS

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 more than 175 days from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]
4	No event and withdrawal of consent date ≥ date of first dose of study treatment date OR end of study (EOS) = Subject refused further follow-up	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a]more than 175 days after last adequate tumor assessment.

PFS = progression free survival; EOS = end of study;

Analyses will be provided based on both the investigator and ICR assessment.

6.2.7. Overall Survival (OS)

OS will be summarized using the Kaplan-Meier method as described in Section 5.2.11. The primary population for analysis will be the DDR Deficient Measurable Disease population.

OS is defined as the time from the date of first dose of study treatment to death due to any cause. Patients who have not died will be censored at the date of last contact.

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

Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median OS with two-sided 95% CIs.

Frequency (number and percentage) of patients with an event and censoring reasons will be presented.

Reasons for censoring will be summarized according to the categories in Table 8. If a patient meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 8. Censoring Reasons and Hierarchy for OS

Hierarchy	Condition	Censoring Reason
1	No event and withdrawal of consent date ≥ date of first dose of study treatment OR EOS = Subject refused further follow-up	Withdrawal of consent
2	No event and lost to follow-up in any disposition page	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

OS = overall survival; EOS = end of study

6.2.8. Patient Reported Outcomes

The primary population for these analyses will be the PRO population. A questionnaire completion table will be provided.

Time to deterioration in patient reported pain as assessed by BPI-SF

Patient-reported pain symptoms (per the Pain Log – BPI-SF Q3) will be completed for 7 consecutive days before each study visit. In addition, the BPI-SF will be completed during each study visit. Four or more completed BPI SF Q3 at each visit period (ie collectively 7 consecutive days prior to each study visit and during study visit) are required for pain score for each time period to be considered evaluable. Pain score averages during each visit period will be calculated and will be used for change from baseline analyses including time to deterioration in patient-reported pain symptoms.

Analgesic use (per Analgesic log) is recorded for seven consecutive days prior to each study visit and during each study visit. The average World Health Organization (WHO) analgesic usage score for each visit period (seven consecutive days prior to each study visit and during study visit) will be calculated and utilized in analyses including time to deterioration in patient-reported pain symptoms. Analgesic use is scored according to WHO criteria: zero for no use, one for use of non-opiate analgesics (eg, non-steroidal anti-inflammatory drugs, acetaminophen, antidepressants, and agents targeting neuropathic pain), two for use of weak opiates for moderate pain (eg, codeine and tramadol), and three for strong opiates for severe pain (eg, morphine and fentanyl). If there is more than one analgesic use in the study visit, then the highest score associated with the analgesics used will be used. Baseline analgesic usage score will be calculated based on concomitant medication data while the postbaseline analgesic usage score will be calculated based on analgesic log.

Time to deterioration in patient-reported pain symptoms per BPI-SF is assessed using the score from the BPI-SF question 3: "Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours." Time to this event is defined as the time from first dose of study treatment to onset of pain progression, where pain progression is defined as a ≥2 point increase from baseline in the question 3 score for two consecutive visit periods at least 4 weeks apart without a decrease in WHO analgesic usage score.

Patients without observed pain progression at the time of analysis will be censored at the date of last BPI-SF assessment.

Kaplan-Meier estimates will be presented together with a summary of associated statistics including the median and quartiles with two-sided 95% CIs.

Frequency (number and percentage) of patients with an event or censoring will be presented.

Descriptive Summaries and Change from Baseline

Descriptive summaries for BPI-SF by visit will be provided. These include:

- For each visit period (collectively for study visit and the 7 consecutive days prior to each study visit), number and percentage of patients who completed all the BPSI-SF Question 3 out of a total of 8), ≥4 of the BPI-SF Question 3, and those who did not complete any BPI-SF Question 3 will be summarized

- Descriptive summary of the average score at each visit period for BPI-SF Question 3

    - Each pain intensity is a whole number (0 through 10) and will be summarized as a continuous variable

    - Missing values (<4 of 8 possible assessments per visit period) are not included in the summaries

Descriptive statistics for change from baseline in patient-reported pain symptoms per BPI-SF (questions 3) will be summarized for each visit period. A graphical display of means over time as well as mean changes from baseline over time will also be provided.

A longitudinal mixed effect model will also be used to summarize the change from baseline pain symptoms score (BPI-SF Question 3) across all visit periods. Unless otherwise specified, all scheduled assessments will be used in the analyses, regardless of adherence to study treatment.

EQ-5D-5L Health Index

Analysis of the EQ-5D health index will consist of descriptive statistics on means and changes from baseline, overall change from baseline using a longitudinal mixed effects model, and graphical displays of means and changes from baseline over time. In addition, there will be a health status profile analysis consisting of a display of the number and

percentage of patients in each of the 5 response levels for each of the 5 dimensions at each visit.

EQ-5D General Health Status (EQ-5D VAS)

Analysis of EQ-5D VAS will consist of descriptive statistics on means and changes from baseline, overall change from baseline using a longitudinal mixed effects model, and graphical displays of means and changes from baseline over time.

6.2.9. Pharmacokinetics

Analyses of the PK data will be conducted using the PK population.

Summary statistics will be provided for pre-dose and post-dose plasma talazoparib concentrations at scheduled visits. Plasma concentration values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. The summary table will include the number of patients, number of samples with values below the limit of quantitation, mean, standard deviation, percent coefficient of variation (%CV), 95% CI, median, minimum, maximum, geometric mean, and geometric %CV.

PK data analyses will include the following endpoints: pre-dose sampling at baseline (week 1/day 1) and weeks 5, 9, and 13, and 2 hours post-dose sampling at week 1/day 1 and week 5. PK data analyses will include descriptive summary statistics of the pre-dose trough and post-dose plasma concentrations for talazoparib by study visit and renal function status.

For this summary, patients from the PK population who meet the following conditions at any of the scheduled visits with PK sample assessments will be included:

- For pre-dose samples, have the sample collected before the next dose administration and 24 hours ± 25% after the last dose administration

- For the 2 hour post-dose samples, have the sample collected within ± 25% of the nominal scheduled time

- For steady-state samples, take at least 10 consecutive daily talazoparib doses without a dose change or interruption

Box and Whiskers plots of talazoparib trough concentrations after multiple doses will be presented by study and/or renal function status using the 'Dose-compliant PK Population' which is defined as follows:

- NORMAL/MILD renal function subjects who started on talazoparib 1 mg and have one or more evaluable PK samples collected within the acceptable collection window from the nominal timepoint (25%) and after at least at least 10-consecutive daily talazoparib doses without a dose change or interruption.

- MODERATE renal function subjects who started on talazoparib 0.75 mg and have one or more evaluable PK samples collected within the acceptable collection window from the

nominal timepoint (25%) and after at least at least 10-consecutive daily talazoparib doses without a dose change or interruption.

Samples collected on week 1/day 1 will be excluded from these Box and Whiskers plots.

A listing of talazoparib concentrations by study visit and timepoint will be generated.

CCI

CCI

CCI

[redacted]

6.4. Subgroup Analyses

All the subgroup analyses will be exploratory. With the exception of the analysis of ORR by mutation status, analyses will only be performed if there is sufficient sample size. The determination of whether or not there is sufficient sample size will be defined after enrollment is complete and prior to database lock. As a general rule, analyses will only be performed if there are ≥20 patients within the defined subset. Deviations from these analyses will be described in the Clinical Study Report.

The following subgroup analyses will be performed for the ORR, PSA response, CTC conversion rate, radiographic PFS and OS by ICR and investigator assessment:

- BRCA1/BRCA2 DNA damage repair gene mutations (other subsets may also be explored in summary tables depending on sample size).

The subgroup analysis of ORR by disease site (visceral vs. non-visceral) will be conducted.

Key safety outputs will be provided to explore the following subgroups:

- DDR Deficient Measurable Disease population
- Renal impairment (moderate, mild, normal)

Moderate renal impairment is defined as eGFR of 30-59 mL/min/1.73 m^2, where eGFR is provided by the central laboratory.

6.5. Baseline and Other Summaries

6.5.1. Baseline Summaries

The following demographic characteristics will be summarized separately for patients in the DDR Deficient Measurable Disease population, for patients from the DDR Deficient Measurable Disease population with BRCA1/BRCA2 mutations, and for patients in safety population:

- Age (continuous and by groups 18-44, 45-64, 65-74, 74-84, >=85),
- Race,
- Ethnicity, and

- Geographic region (North America, European Union, rest of world)

The following baseline disease characteristics will be summarized separately for all patients in the DDR Deficient Measurable Disease population, for patients from the DDR Deficient Measurable Disease population with BRCA1/BRCA2 mutations, and for patients in safety population:

- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Baseline serum PSA (ng/mL)
- Baseline use of a bone targeting agent (yes/no)
- Gleason score (Grade Group 1 [6 or less], Grade Group 2 [3+4=7], Group 3 [4+3=7], Group 4 [8], Group 5 [9 or 10])
- TNM stage
- Testosterone level at baseline
- Bone metastases at baseline (yes/no)
- Visceral disease (yes/no)
- Baseline pain score by brief pain inventory question 3 (0-1, 2-3, >3)
- Baseline eGFR(normal, mild, moderate),
    - normal, mild, and moderate are defined based on baseline eGFR of >90 mL/min/1.73 m^2, 60-89 mL/min/1.73 m^2, and 30-59 mL/min/1.73 m^2 respectively.
- Prior New Hormonal Agent
- Prior Taxane Use
- Site of Metastases
- Type of Progression at Study Entry
- Time since initial diagnosis of prostate cancer, defined as the time from date of first dose to date of diagnosis, and
- Baseline CTC count
    - Continuous summary
    - Categorical summary (≥5 CTC per 7.5 mL of blood, <5 CTC per 7.5 mL of blood, ≥1 CTC per 7.5 mL of blood, 0 CTC per 7.5 mL of blood)

Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's SOC and PT for all patients in the safety population. Each patient will be counted only once within each PT or SOC. Summaries will be ordered by primary SOC and PT in descending order of frequency. Separate summaries will be provided for past and present conditions.

Prior Anti-Cancer Treatments

Prior anti-cancer treatments include systemic therapy, radiation, and surgery.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated for patients in the DDR Deficient Measurable Disease population:

- Patients with at least one prior anti-cancer drug therapy;
- Patients with at least one prior anti-cancer radiotherapy;
- Patients with any androgen deprivation therapy;
- Patients with prior continuous androgen deprivation therapy;
- Patients with prior intermittent androgen deprivation therapy.

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

- Number of prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / ≥4.

The prior anti-cancer drugs will be coded in the WHO Drug coding dictionary and will be summarized based on the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) medication class and preferred term. A patient will be counted only once within a given preferred term, even if he received the same medication at different times. The summary will be sorted on decreasing frequency. In case of equal frequency, alphabetical order will be used.

Prior Surgeries

A summary of the number of patients with the following surgeries will be provided:

- Prostatectomy
- TURP
- Prostate biopsy
- Orchiectomy

- Pelvic node dissection, or
- Renal stenting

Specific details on all other surgeries will be listed.

6.5.2. Study Conduct and Patient Disposition

6.5.2.1. Patient Disposition

A summary of the number of patients enrolled by country and site will be provided for the DDR Deficient Measurable Disease population and the safety population separately.

Discontinuation for each epoch will be summarized separately. Discontinuations will be summarized using the safety population and the DDR Deficient Measurable Disease population separately.

6.5.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and will be summarized by category (n[%]) for the safety population. Categories will be assigned by the study team.

A separate summary of inclusion and exclusion criteria deviations will also be provided for DDR Deficient Measurable Disease population.

6.5.2.3. Tissue Sample Results for Enrollment

A summary of molecular biology disease sample tests including the following information as reported on the molecular biology of disease (MBIO) tumor tissue CRF pages will be provided for all screened patients:

- Site of tissue collection (bladder; lung; bone; lymph node; kidney; liver; prostate gland; brain; rectum; urethra; other)
- Biopsy sample form (slides; paraffin block)
- Sample collection procedure (core needle biopsy; excisional biopsy; resection; unknown; other)
- Age of sample
    - Age of sample is defined as the time from date of sample collection to date of sample analyzed

The number and percentage will be provided for de novo tissues and archival tissues separately, where the percentages will be calculated based on the total number of samples in each type of tissue. Separate summaries will be provided by mutation status (DDR deficiencies patients vs non DDR-deficient patients vs patients with unknown mutation status).

A summary of mutation type will be provided based on central laboratory and historical results CRF separately for DDR Deficient Measurable Disease population, and the safety population and will include the number and percentage of patients in each mutation type. Summary of mutation include genes noted in Section 5.2.6 and mutations from the expanded gene panel.

6.5.3. Study Treatment Exposure

Exposure will be summarized separately for the safety population and the DDR Deficient Measurable Disease population.

The daily dose of talazoparib is 1 mg/day given orally at approximately the same time each day. The starting dose will be 0.75 mg/day for patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2).

Summary of treatment exposure will include the following:

- Treatment duration (months): For each patient, treatment duration is defined as (date of last dose – date of first dose + 1) / 30.4375. Treatment duration will be summarized both as a continuous measure and a categorical measure (≤3 months, 3 to <6 months, 6 to <12 months, ≥12 months).

- Average daily dose (mg/day): The average daily dose is defined as the cumulative dose divided by the dose exposure, where cumulative dose is the sum of the actual dose levels that the patient received.

- Dose intensity (mg/week): Dose intensity is defined as the cumulative dose divided by the treatment duration in weeks.

- Relative dose intensity (RDI, %): Relative dose intensity is defined as the ratio of the dose intensity and the planned intensity expressed in %. The planned dose intensity will be 7 mg (1 mg per day for 7 days) for patients without moderate renal impairment and 5.25 mg (0.75 mg per day for 7 days) for patients with moderate renal impairment.

  RDI (%) = 100x[dose intensity (mg/week)]/[planned dose intensity(mg/week)].

A dose reduction is defined as a non-zero dose that is less than the prior dose.

The number and percentage of patients with at least one dose reduction as well as a breakdown of dose reductions will be summarized. Reasons for dose reductions will also be summarized. Patients can contribute to more than one reason if multiple dose reductions occurred for different reasons but will only be counted once per reason. Percentages will be calculated based on the total number of patients in safety population.

An interruption is defined a 0 mg dose. (Note: 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. Patients can contribute to more than one

reason if multiple dose interruptions occurred for different reasons but will only be counted once per reason. Percentages will be calculated based on the total number of patients in safety population.

A summary of the total duration (days) of dose interruptions due to adverse event for each patient will also be provided where 'n' is the number of dose interruptions. An individual can contribute multiple observations, one for each interruption.

Time to first interruption (weeks) and time to first reduction (weeks), measured from the date of first dose of study treatment, will be summarized for patients who had at least one interruption or reduction respectively.

6.5.4. Concomitant Medications and Non-Drug Treatments

Concomitant medications and non-drug treatments received by patients during the study will be summarized for the safety population.

Concomitant medications refer to all medications which started prior to first dose of study treatment and continued during the on-treatment period (see Section 3.5) as well as those started during the on-treatment period. Concomitant medications will be coded in the WHO Drug coding dictionary and will be tabulated by ATC Classification level 2 and preferred term in descending order of frequency. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. A patient will be counted only once within a given drug class and within a given drug name, even if he received the same medication at different times. Preferred terms will be reported under each ATC class that it is included under within WHO Drug (no primary path is available in WHO Drug).

The concomitant medication CRF page collects both general concomitant medications as well as analgesics. Separate summaries will be provided for general concomitant medications and analgesics. Additionally, a separate summary of concomitant analgesics with onset prior to first dose of study treatment will be provided.

Concomitant non-drug treatments refer to all non-drug treatments administered during the on-treatment period. Non-drug treatments will be coded in MedDRA and will be summarized by MedDRA's SOC and PT in descending order of frequency. Patients will be counted only once per PT even if he/she received the same treatment multiple times.

A separate summary of blood product transfusions will be provided.

Any medications or non-drug treatments, aside from anti-cancer treatments, which were only administered prior to treatment start will be listed but not summarized.

6.5.5. Subsequent Anti-Cancer Therapies/Procedures

Subsequent anti-cancer therapies and procedures are defined as therapies entered on the 'Follow-up Cancer Therapy' or the log 'Radiation Therapy', and 'Surgery' CRF pages where the date is on or after the date of first dose of study treatment. The number and percentage of patients within each category (medication therapy, radiation therapy, and surgeries) will be provided for DDR Deficient Measurable Disease population.

Medications will be coded using the WHO Drug coding dictionary and will be tabulated by SOC and PT in descending order of frequency.

6.6. Safety Summaries and Analyses

Unless otherwise specified, summaries of AEs and other safety parameters will be based on the safety population. Additional subgroup analyses will be provided for a subset of tables based on the populations described in Section 6.4.

6.6.1. Adverse Events

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.5. AEs not considered treatment emergent will be flagged in data listings. AE will be reported based on Oracle Clinical Remote Data Capture (OCRDC) unless otherwise specified.

A high-level summary of adverse events will be provided separately for the safety population and the subgroups defined in Section 6.4 and will include the number and percent of patients with:

- Any adverse event;
- Serious AE;
- Adverse events with NCI-CTCAE Grade 3-4;
- Grade 5 events;
- AEs leading to dose interruptions of talazoparib;
- AEs leading to dose reductions of talazoparib; and
- AEs leading to permanent withdraw of talazoparib.

Additionally, the number of events reported for each of the categories above will be provided. Each unique adverse event at the PT level for a patient is included in the count.

Seriousness, toxicity grade, action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries by SOC and PT in decreasing frequency based on the frequencies will be provided for the safety population and the subgroups specified in Section 6.4 as follows:

- Treatment emergent events (all causality);
- Treatment emergent events by maximum toxicity grade (all causality);
- Treatment emergent events (treatment related);

- Treatment emergent events by maximum toxicity grade (treatment related);
- Serious treatment emergent events (all causality);
- Serious treatment emergent events (treatment related).

An event will be considered treatment related if the investigator considered the event related to one or both of study drugs given in combination.

The following summaries will be provided by PT only (ie summaries will not include SOC) in decreasing frequency based on the frequencies separately for the safety population and the subgroups specified in Section 6.4 as follows:

- Treatment emergent events (all causality) experienced by ≥10% of patients;
- Treatment emergent events (treatment related) experienced by ≥10% of patients
- Treatment emergent events (all causality) by preferred term and maximum toxicity Grade experienced by ≥10% of patients;
- Treatment emergent events (treatment related) by preferred term and maximum toxicity Grade experienced by ≥10% of patients;
- Treatment emergent adverse events leading to dose interruptions of talazoparib (all causality);
- Treatment emergent adverse events leading to dose reductions of talazoparib (all causality);
- Treatment emergent adverse events leading to permanent discontinuation of talazoparib (all causality);
- Serious treatment emergent events (all causality)
- Serious treatment emergent events (treatment related).

Each patient will be counted only once within each SOC and PT. In case a patient has events with missing and non-missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed if only one event has been reported for a patient and the grade is missing.

A listing of SAE from Argus will be provided for the safety population.

6.6.1.1. Adverse Events of Special Interest

The following identified risks and general safety events will be summarized for separately the safety population and the subgroups specified in Section 6.4.

- AML
- MDS
- Venous Thrombotic Events (VTE)
- Pneumonitis, and
- Second primary malignancies (other than hematologic)

These events will be defined based on a list of MedDRA Preferred Terms specified prior to database release.

Separate summaries for each AESI will be provided by maximum toxicity and will include an 'any event' row along with a row for each contributing PT in descending order of frequency.

Given the observed incidence of hematologic toxicities associated with the use of talazoparib, a summary of hematologic AEs will be providing showing the incidence of the following cluster terms:

- ANEMIA: anaemia, decreased hemoglobin, decreased hematocrit, or red blood cell count decreased
- NEUTROPENIA: neutropenia or decreased neutrophil count
- THROMBOCYTOPENIA: thrombocytopenia or platelet count decreased
- LEUKOPENIA: leukopenia or white blood cell count decreased
- LYMPHOPENIA: lymphopenia or lymphocyte count decreased

Additionally, a summary of the number and percentage of patients who reported MDS or AML as recorded on the cancer assessment page will be provided for the safety population.

6.6.2. Deaths

The frequency (number and percentage) of patients who died and who died within 28 days after last dose of study treatment as well as the primary reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' CRFs will be summarized separately for the safety population and DDR Deficient Measurable Disease population.

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).

Fatal adverse events will be listed for the safety population.

6.6.3. Laboratory Data

Summaries of laboratory results will be provided for the safety population only.

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying toxicity grades and for all summaries.

Quantitative data will be summarized using simple descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie unscheduled assessments will be excluded). Summary will only include data from central laboratories. The total number of patients for change from baseline will include all patients who have both a baseline value and a value at the nominal visit.

As described in Section 3.4, baseline will be defined as the last assessment performed on or prior to date of the first dose of study treatment. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade.

Results collected as strict inequalities (eg, >10, <10) will be converted to numeric values subtracting a factor of <0.001>. Expressions of the form" ≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities but will not be included in calculations of summary statistics.

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 4.03 grades. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (eg hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of patients corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (eg NCI- CTCAE grading criteria for creatinine increased – a value can fall into one range based on comparison to Upper Limit of Normal (ULN) and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the NCI-CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically by in the NCI-CTCAE guidance. However, programmatically this is used as a category to represent those patients who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for NIC-CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading) and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Abnormalities will be described using the worst grade by scheduled timepoint and overall. Worst grade by scheduled timepoint will be determined using only central laboratory results. Worst case overall will be determined using both central and local laboratory results from

scheduled and unscheduled visits. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 hypercalcemia will be classified as a Grade 0 hypocalcemia. For NCI-CTCAE terms that can be derived using one of several laboratory tests, the maximum post-baseline grade for a given patient and NCI-CTCAE term will be the maximum across all possible laboratory tests.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the following categories by scheduled timepoint as well as overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given patient, clinically significant abnormalities are noted in both directions (eg, >ULN and <Lower Limit of Normal [LLN]), then both abnormalities are counted. Summaries at schedule timepoints will consider only central laboratory data; however, summaries overall will consider both central and local laboratory data.

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over the 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:

- ALT ≥3×ULN, ALT ≥5xULN, ALT ≥10×ULN, ALT ≥20×ULN,
- AST ≥3×ULN, AST ≥5xULN, 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, and
- 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.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols, by graphically displaying:

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN,
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI ≥2×ULN, ALT≥3×ULN or AST ≥3×ULN will be provided.

6.6.4. Vital Signs

Vital signs data includes weight, temperature, systolic blood pressure, diastolic blood pressure, and heart rate. Summaries will be provided for the safety population only.

Vital signs data will be summarized using simple descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie unscheduled assessments will be excluded). The total number of patients for change from baseline will include all patients who have both a baseline value and a value at the nominal visit. Baseline will be selected as defined in Section 3.4.

All recorded vital sign data will be listed.

The number and percentage of patients with the following vital sign changes will be presented. The definitions of potentially clinically significant abnormalities are shown in Table 9.

Table 9. Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Criteria for Potentially Clinically Significant Abnormalities
Systolic blood pressure	Absolute result >180 mm Hg and increase from baseline ≥40 mm Hg
	Absolute result <90 mm Hg and decrease from baseline >30 mm Hg
Diastolic blood pressure	Absolute result >110 mm Hg and increase from baseline ≥30 mm Hg
	Absolute result <50 mm Hg and decrease from baseline >20 mm Hg
	≥20 mm HG increase from baseline
Heart Rate	Absolute result >120 bpm and increase from baseline >30 bpm
	Absolute result <50 bpm and decrease from baseline >20 bpm
Weight	>10% decrease from baseline

bpm = beats per minute; mm Hg = millimeters of mercury

6.6.5. Electrocardiogram

Electrocardiogram (ECG) findings will be listed for the safety population.

6.6.6. ECOG Performance Status

The ECOG performance status will be listed for the DDR Deficient Measurable Disease population.

6.6.7. Physical Examination

Physical examination findings will be listed for the safety population.

6.6.8. Medication Errors

Medication errors for study treatment include overdose, lack of dose reduction, continuation of treatment after discontinuation criteria met, and incorrect dosage taken. Medication errors will be listed for the safety population.

7. INTERIM ANALYSES

As described in Section 5.1 there will be 4 analysis timepoints:

- an analysis after 20 DDR Deficient Measurable Disease patients receive study treatment for at least 8 weeks;
- an analysis after 20 BRCA1/BRCA2/PALB2 patients with measurable disease receive study treatment for at least 16 weeks or are otherwise no longer being followed (ie have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up);
- an analysis after 60 DDR Deficient Measurable Disease patients complete at least 6 months of study treatment or are otherwise no longer being followed (ie have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up);
- a final analysis after 100 DDR Deficient Measurable disease patients complete at least 6 months of study treatment or are otherwise no longer being followed (ie have withdrawn consent, discontinued from the study, died, or are otherwise lost to follow-up).

The summaries for the initial analyses will include a subset of the CSR safety and efficacy summaries as specified in the list of tables for each analysis.

8. REFERENCES

1. Brookmeyer R, Crowley JJ. A confidence interval for median survival time. Biometrics. 1982 Mar;38 (1):29-41.
2. Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 26: 404–413.
3. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline version 1.1. Eur J Can 45: 228-47, 2009.
4. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

5. National Cancer Institute (NCI). Common Terminology Criteria For Adverse Events (CTCAE). http://evs.nci.nih.gov/ftp1/CTCAE/About.html

ABBREVIATIONS

ADP	Adenosine Diphosphate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Level of Quantification
BOR	Best Overall Response
BPI-SF	Brief Pain Inventory Short Form
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Axial Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CV	Coefficient Variation
DDR	Deoxyribonucleic Acid Damage Repair
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5-Domain 5-Level Scale
ICR	Independent Central Review
IOTA	Investigator Overall Objective Tumor Assessment
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MBIO	Molecular Biology of Disease
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NC	Not Calculated
NCI	National Cancer Institute
ND	Not Done

NE	Not Evaluable
NHT	Novel Hormonal Therapy
NR	Not Reached
NS	No Sample
OCRDC	Oracle Clinical Remote Data Capture
ORR	Overall/Objective Response Rate
OS	Overall Survival
OTR	Outside Toxicity Reference
PARP	Poly (adenosine diphosphate [ADP]-ribose) Polymerase
PCWG3	Prostate Cancer Working Group 3
PD	Progressive Disease/Disease Progression
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PRO	Patient-Reported Outcome
PSA	Prostate-Specific Antigen
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TBILI	Total Bilirubin
TTR	Time to Response
TURP	Transurethral Resection of the Prostate
ULN	Upper Limit of Normal
WHO	World Health Organization