PROTOCOL C3441021

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Talazoparib With Enzalutamide in Metastatic Castration-Resistant Prostate Cancer

Statistical Analysis Plan

(SAP)

Version: 6.2

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3441021 is based on the Protocol Amendment #8 dated 17-JUN-2021.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1	Protocol Amendment 2 30 October 2018	N/A (Final SAP not provided for pervious protocol versions)	N/A
2	Protocol Amendment 4 22 July 2019	The primary purpose of the SAP revision is to align with Protocol Amendment 4.	• The number of patients for the all-comers cohort was increased from 560 to 750 • The interim analyses were adjusted to align with the updated timeline for the all-comers cohort • The derivation of objective response by investigator review was clarified • Updated the treatment-emergent algorithm • Other changes were incorporated to provide clarification for the programming team
3	Protocol Amendment 6 26 February 2020	The primary purpose of the SAP revision is to align with Protocol Amendment 6.	• Liquid biopsy was introduced to assess the patients' tumor DDR status at pre-screening or screening. Concordance of DDR testing results between liquid and tumor tissue biopsies was added as exploratory endpoint. Both samples had to be provided prior to randomization. • Other minor changes were incorporated for clarification.
4	Protocol Amendment 7 18 September 2020	The primary purpose of the SAP revision is to align with Protocol amendment 7 and also add sensitivity analyses to assess the impact of COVID-19.	• Data from the China extension cohort will be analyzed separately per local regulatory requirement. • Additional analyses were added to assess the impact of COVID-19. • Other changes were incorporated for clarification.
5	Protocol Amendment 8 17 June 2021	To align with Protocol amendment 8.	• Updated the first interim analysis (for futility) and introduced a second interim analysis (for efficacy) for the DDR-deficient cohort. • Updated the definition of PFS2.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Other minor changes were incorporated to provide clarification.
6	Protocol Amendment 8 17 June 2021	The primary purpose of the SAP revision is to clarify several analyses.	• The definitions of DDR mutational status were clarified. • Subgroup analyses of the primary endpoint were specified. • Added 2-sided p-values for efficacy analysis tables.
6.1	Protocol Amendment 8 17 June 2021	The primary purpose of the SAP revision is to update the adverse events of special interest for enzalutamide and provide further clarifications to the analysis of PRO data.	• The list of AESIs for enzalutamide was updated after consultation with the FDA. • Additional clarifications for the analysis of PRO data were provided. • The definitions of cytotoxic chemotherapy and antineoplastic therapy were updated.
6.2	Protocol Amendment 8 17 June 2021	The primary purpose of the SAP revision is to clarify the definition of DDR status and the corresponding subgroup analyses.	• The definition of DDR status has been clarified. • The subgroup analysis based on DDR status has also been clarified.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3441021, a two-part Phase 3 study of patients with metastatic castration resistant prostate cancer (mCRPC) where no systemic cancer treatments have been initiated after documentation of the CRPC state. This SAP does not describe the analyses for the molecular profiling as those will be provided in a separate analysis plan.

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).

There are two parts in this study:

- Part 1 was open-label and non-randomized and evaluated the safety, tolerability, and pharmacokinetics (PK) of talazoparib in combination with enzalutamide. Nineteen mCRPC patients were enrolled to establish the appropriate starting dose of talazoparib in combination with enzalutamide for Part 2.

- Part 2 is randomized, double-blind, and placebo controlled and will evaluate the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide. Part 2 will enroll two patient cohorts. Cohort 1 will enroll approximately 750 mCRPC patients unselected for deoxyribonucleic acid (DNA) damage repair (DDR) status (all-comers population). After enrollment in Cohort 1 is complete, enrollment will continue but will be restricted to patients with DDR-deficient mCRPC (Cohort 2). Cohort 2 will enroll approximately 268 additional patients whose disease has DDR gene mutations likely to sensitize to Poly (adenosine diphosphate [ADP]-ribose) Polymerase (PARP) inhibition (DDR-deficient). Patients whose tumors are DDR-deficient from Cohorts 1 and 2 will be combined such that a total of approximately 380 patients with DDR-deficient mCRPC (referred to as "DDRdeficient- population") are enrolled to assess efficacy within this group. For details see Figure 1.

The primary analysis in the all-comers population (Cohort 1) will include all data up to a data cutoff date that will be determined when approximately 333 radiographic progression-free survival (rPFS) events are observed in this population. At this time, a futility interim analysis will be performed in the DDR-deficient population. All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cutoff date. The primary analysis in the DDR-deficient population will be performed when 224 rPFS events are observed in this population.

Data from Part 1 will be summarized to confirm the dose prior to initiating Part 2. Final summaries of Part 1 data will be provided after additional follow-up.

Throughout the SAP the terms antineoplastic therapy and anticancer therapy are used interchangeably to account for different terminology utilized with endpoints within prostate cancer and standard CRF language.

2.1. Study Objectives, Endpoints, and Estimands

2.1.1. Objectives and Endpoints in Part 1 (Open-Label Treatment)

Type	Primary Objective(s):	Primary Endpoint(s):	Definition	Analysis and Summary
Safety	• To determine the starting dose of talazoparib when given in combination with enzalutamide during Part 2 (double-blind treatment period).	• Occurrence of target safety events.	Section 3.1.1	Section 6.1.1
	Secondary Objective(s):	**Secondary Endpoint(s):**		
PK	• To characterize the steady state PK of talazoparib and enzalutamide and its N-desmethyl metabolite when given in combination.	• Multiple-dose PK parameters of talazoparib and enzalutamide and its N-desmethyl metabolite (Multiple-dose C_{max}, C_{trough}, T_{max}, AUC_{τ} and CL/F as data permit).	Section 3.1.2	Section 6.1.2
	Exploratory Objective(s):	**Exploratory Endpoint(s):**		
PD	• To explore correlation of changes in CTCs with efficacy outcome parameters.	• Proportion of patients with conversion from 5 or more CTCs per 7.5 mL at baseline to 4 or fewer CTCs per 7.5 mL post-baseline. • Proportion of patients with conversion from detectable CTCs per 7.5 mL at baseline to CTCs = 0 per 7.5 mL post-baseline. • Proportion of patients with baseline CTCs <5 who show increased CTCs post-baseline.	Section 3.1.3	No analysis planned for CSR.
	• To identify potential biomarkers associated with response and/or resistance to talazoparib in combination with enzalutamide.	• Molecular profiling of tumor tissue remaining after genomic testing for eligibility and of saliva and ctDNA; circulating protein biomarker profiles.	NA	No analysis planned for CSR
	• To explore correlations between talazoparib/enzalutamide exposure and biomarker, efficacy and safety outcome parameters if data allow.	NA	NA	No analysis planned for CSR
Other	• To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	• Potential results from exploratory analyses of banked biospecimens.	NA	No analysis planned for CSR

CTCs = circulating tumor cells; NHT = novel hormonal therapy; PK = pharmacokinetics.

2.1.2. Objectives and Endpoints in Part 2 (Double-Blind Treatment)

Type	Primary Objective(s):	Primary Endpoint(s):	Definition	Analysis and Summary
Efficacy	To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging BICR assessed rPFS, in patients with mCRPC unselected for DDR status.	BICR assessed rPFS per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients with mCRPC unselected for DDR status.	Section 3.2.1.1	Section 6.2.1
	To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging BICR assessed rPFS, in patients with mCRPC harboring DDR deficiencies.	BICR assessed rPFS per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.1	Section 6.2.1
	Secondary Objective(s):	**Secondary Endpoint(s):**		
	Key Secondary Objective:	**Key Secondary Endpoint:**		
Efficacy	To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging OS in patients with mCRPC unselected for DDR status.	OS in patients with mCRPC unselected for DDR status (alpha-protected).	Section 3.2.1.2	Section 6.2.2.1
	To demonstrate that talazoparib in combination with enzalutamide is superior to placebo in combination with enzalutamide in prolonging OS in patients with mCRPC harboring DDR deficiencies.	OS patients with mCRPC harboring DDR deficiencies (alpha-protected).	Section 3.2.1.2	Section 6.2.2.1

Type	Primary Objective(s):	Primary Endpoint(s):	Definition	Analysis and Summary
	Other Secondary Objectives:	**Other Secondary Endpoints:**		
Efficacy	To evaluate antitumor activity in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies with respect to the following:			
	BICR assessed objective response in measurable soft tissue disease;	Proportion of patients with measurable soft tissue disease at baseline with an objective response per RECIST 1.1 (assessed by BICR) in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.3	Section 6.2.2.2
	BICR assessed duration of response in measurable soft tissue disease;	Duration of soft tissue response per RECIST 1.1 (assessed by BICR) in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.4	Section 6.2.2.3
	PSA response;	Proportion of patients with PSA response ≥50% in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.5	Section 6.2.2.4
	Time to PSA progression;	Time to PSA progression in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.6	Section 6.2.2.5
	Time to initiation of cytotoxic chemotherapy;	Time to initiation of cytotoxic chemotherapy in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.7	Section 6.2.2.6
	Time to initiation of antineoplastic therapy;	Time to initiation of antineoplastic therapy in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.8	Section 6.2.2.7
	Time to first symptomatic skeletal event;	Time to first symptomatic skeletal event in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.9	Section 6.2.2.8
	PFS on next line therapy (PFS2);	PFS2 based on investigator assessment separately in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.10	Section 6.2.2.9

Type	Primary Objective(s):	Primary Endpoint(s):	Definition	Analysis and Summary
	Opiate use for prostate cancer pain.	Time to opiate use for prostate cancer pain in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.1.11	Section 6.2.2.10
Safety	To evaluate safety of talazoparib and enzalutamide administered in combination.	Incidence of adverse events characterized by type, severity (graded by NCI CTCAE version 4.03), timing, seriousness and relationship to study treatment.	Section 3.4	Section 6.5
PK	To evaluate the PK of talazoparib and enzalutamide (and its N-desmethyl metabolite) when dosed in combination.	PK characterized by pre-dose trough and post-dose plasma concentrations of talazoparib, enzalutamide and its N-desmethyl metabolite.	Section 3.2.2	Section 6.2.4
PRO	To evaluate the following patient-reported outcomes in each treatment arm in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies:			
	Pain symptoms;	Change from baseline in patient-reported pain symptoms per BPI-SF; Time to deterioration in patient-reported pain symptoms per BPI-SF;	Section 3.2.4	Section 6.2.3
	Cancer-specific global health status/QoL, functioning, and symptoms outcomes;	Time to definitive deterioration in patient-reported global health status/QoL per EORTC QLQ-C30; Time to definitive deterioration in patient-reported disease-specific urinary symptoms per EORTC QLQ-PR25.		
	General health status.	Change from baseline in patient-reported general health status per EQ-5D-5L; Change from baseline in patient-reported cancer-specific global health status/QoL, functioning, and symptoms per EORTC QLQ-C30;		
	Exploratory Objective(s):	**Exploratory Endpoint(s):**		
Efficacy	To explore BICR assessed rPFS in patients with mCRPC without DDR deficiencies.	BICR assessed rPFS per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients with mCRPC without DDR deficiencies.	Section 3.2.1.1	Section 6.2.1
PD	To explore correlation of changes in CTCs with efficacy outcome parameters.	Proportion of patients with conversion from 5 or more CTCs per 7.5 mL at baseline to 4 or fewer CTCs per 7.5 mL post-baseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.	Section 3.2.3	Section 6.2.5

Type	Primary Objective(s):	Primary Endpoint(s):	Definition	Analysis and Summary
		Proportion of patients with conversion from detectable CTCs at baseline to CTCs = 0 per 7.5 mL post-baseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies. Proportion of patients with baseline CTCs <5 who show increased CTCs post-baseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies.		
	To identify potential biomarkers associated with response and/or resistance to talazoparib in combination with enzalutamide.	• Molecular profiling of tumor tissue remaining after genomic testing for eligibility and of saliva and ctDNA; circulating protein biomarker profiles.	NA	No analysis planned for CSR
	To explore correlations between talazoparib exposure and biomarker, efficacy and safety endpoints if data allow.	NA	NA	No analysis planned for CSR
Other	To collect banked biospecimens for exploratory research, unless prohibited by local regulations or ethics committee decision.	Molecular profiles of tumor tissue remaining after genomic testing for eligibility during prescreening/screening, and of saliva and, of ctDNA; circulating protein biomarker profile. Potential results from exploratory analysis of banked biospecimens.	NA	No analysis planned for CSR
	To explore the concordance of DDR deficiency results between blood and tumor tissue based tests.	Concordance of DDR deficiency results between blood and tumor tissue based tests.	NA	Section 6.2.5.3

ctDNA = circulating tumor DNA; CTCAE = Common Toxicity Criteria for Adverse Events; CTCs = circulating tumor cells; DDR = DNA damage repair; EORTC = European Organisation for Research and Treatment of Cancer; QLQ-PR25; EORTC Quality-of-Life Cancer Questionnaire Prostate Cancer Module; EQ-5D-5L = European Quality-of-Life 5-Domain 5-Level Scale; NCI = National Cancer Institute; PFS = progression-free survival;
PK = pharmacokinetics; PSA = prostate-specific antigen; QLQ-C30 = Quality-of-Life Cancer Questionnaire.

2.2. Study Design

This is an international, Phase 3, two-part study enrolling patients with mCRPC where no systemic cancer treatments have been initiated after documentation of the CRPC state.

Part 1 was open-label and non-randomized and evaluated the safety, tolerability, and PK of talazoparib in combination with enzalutamide. Nineteen mCRPC patients were enrolled to establish the appropriate starting dose of talazoparib in combination with enzalutamide for Part 2.

Part 2 is randomized, double-blind, and placebo-controlled and will evaluate the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide. Part 2 will enroll two patient cohorts.

Cohort 1 will enroll approximately 750 mCRPC patients unselected for DDR status (all-comers population). Although patients will be unselected for DDR status, genomic screening prior to randomization is required for stratification.

Once enrollment in Cohort 1 is complete, enrollment will continue but will be restricted to patients whose disease has DDR gene mutations likely to sensitize to PARP inhibition (Cohort 2). Approximately 268 additional patients whose disease has DDR gene mutations likely to sensitize to PARP inhibition (DDR-deficient) will be enrolled into Cohort 2. A total of approximately 380 patients with DDR-deficient mCRPC are expected to enroll in Cohorts 1 and 2; they will be combined for the purpose of assessing efficacy and safety in the DDR-deficient population.

Approximately 1037 men (19 in Part 1 and approximately 1018 in Part 2) with mCRPC will be enrolled. Genomic screening to identify alterations in DDR genes is optional for patients in Part 1, but is required for randomization in Part 2. Mutational status will be determined by testing for the presence of mutations in defined DDR genes likely to sensitize to PARP inhibition using next generation sequencing (NGS) based gene panel test.

A patient will participate in up to 5 periods: prescreening (optional), screening, Part 1 (open-label) or Part 2 (double-blind), safety follow-up, and long-term follow-up. Testing for DDR gene alterations will be performed at prescreening or screening.

Patients randomized into Part 2 will receive talazoparib or identical placebo at a starting dose of 0.5 mg/day in combination with enzalutamide 160 mg/day. Patients with moderate renal impairment at screening (eGFR 30-59 mL/min/1.73 m^2) will receive talazoparib or identical placebo capsules at a reduced starting dose of 0.35 mg/day. Study treatment (including enzalutamide) should continue until radiographic progression is determined by BICR (Part 2) or local review (Part 1), unless in the opinion of the investigator the patient is still deriving benefit at this time, or following radiographic progression the patient is then no longer clinically benefitting in the opinion of the investigator, or an adverse event leading to permanent discontinuation, or patient decision to discontinue treatment, or death.

2.2.1. China-specific Extension

Per China's registration requirement, at least 113 mCRPC patients from China need to be enrolled into the study.

Given that global enrollment in Cohort 1 of TALAPRO-2 will be completed prior to the randomization of 113 patients from China, additional all-comer patients will continue to be randomized in a China extension cohort after completion of enrollment into Cohort 1. The China extension cohort will enroll concurrently with Cohort 2 of the study, but patients enrolled in Cohort 2 will not contribute to the China extension cohort.

Patients enrolled in the China extension cohort will be analyzed for the purpose of registration in China only. Data analysis of the global trial will not include patients enrolled in the China extension cohort.

Patients enrolled in China in Cohort 1 and in the China extension cohort will be pooled together to form the China cohort. Data from the China cohort will be analyzed separately per local regulatory requirement in China and reported in a separate document. Further details are provided in Section 8.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Part 1

3.1.1. Primary Endpoint

The **occurrence of target safety events** will be evaluated to determine the starting dose of talazoparib for Part 2. The definition of target safety events are presented in Section 6.1.1.

3.1.2. Secondary Endpoints

Multiple-dose PK parameters of talazoparib and enzalutamide and its N-desmethyl metabolite: multiple-dose Cmax, Ctrough, Tmax, AUCτ, and CL/F as data permits. PK data analyses will include predose sampling as well as sampling at 1, 2, 4, 6 and 24 hours postdose at Day 1 (week 1) and week 9. Additionally, blood samples for PK are collected at predose and 2 hours postdose at week 5 and predose at weeks 13 and 17. The PK data may be pooled with data from Part 2 to develop a population PK model. The correlations between talazoparib exposure parameters in combination with enzalutamide and biomarker, efficacy, and safety endpoints will be explored if data allows. The results of these modeling analyses will be reported separately from the clinical study report.

3.1.3. Exploratory Endpoints

Proportion of patients with conversion from 5 or more CTCs per 7.5 mL at baseline to 4 or fewer CTCs per 7.5 mL postbaseline. CTC counts ≥ 5 CTCs per 7.5 mL of blood will be considered unfavorable and CTC counts ≤ 4 CTC per 7.5 mL of blood will be considered favorable. Patients with a CTC count < 5 per 7.5 mL of blood at baseline will not be analyzed for this conversion endpoint. CTC counts will be assessed as a candidate pharmacodynamic biomarker and/or predictive biomarker of response and/or resistance.

Proportion of patients with conversion from detectable CTCs per 7.5 mL at baseline to CTCs = 0 per 7.5 mL postbaseline. Patients with a CTC count of 0 per 7.5 mL of blood at baseline will not be analyzed for this conversion endpoint.

Proportion of patients with baseline CTCs <5 who show increased CTCs postbaseline. Patients with a CTC count of ≥ 5 per 7.5 mL of blood at baseline will not be analyzed for this conversion endpoint.

Molecular profiling of tumor tissue remaining after genomic testing for eligibility and of saliva and circulating tumor DNA (ctDNA); circulating protein biomarker profiles.

3.2. Part 2

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Endpoints

- BICR assessed rPFS per Response Evaluation Criteria in Solid Tumors v1.1 (RECIST 1.1) (soft tissue disease) and Prostate Cancer Working Group 3 (PCWG3) (bone disease) in patients with mCRPC unselected for DDR status

- BICR assessed rPFS per RECIST 1.1 (soft tissue disease) and PCWG3 (bone disease) in patients with mCRPC harboring DDR deficiencies

CCI [redacted]

Radiographic PFS (rPFS) is defined as the time from the date of randomization to the date of the first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone (upon subsequent confirmation) per PCWG3 guidelines, or death, whichever occurs first. The same definition applies to both BICR and investigator assessed rPFS. CCI [redacted]

3.2.1.2. Key Secondary Endpoints CCI [redacted]

- OS in patients with mCRPC unselected for DDR status CCI [redacted]

- OS in patients with mCRPC harboring DDR deficiencies (alpha protected)

3.2.1.3. Proportion of Patients with Measurable Soft Tissue

Proportion of patients with measurable soft tissue disease at baseline with an objective response per RECIST 1.1 in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the proportion of patients with a best overall confirmed soft tissue response of complete response (CR) or partial response (PR) according to RECIST 1.1. Soft tissue responses must be confirmed by a follow-up radiographic assessment at least 4 weeks later with no evidence of confirmed bone disease progression on repeated bone scans at least 6 weeks apart per PCWG3 criteria. Patients without documented CR or PR will be considered non-responders. The primary evaluation of objective response rate (ORR) will be based on BICR overall tumor assessment. An evaluation of ORR based on derived investigator assessment using RECIST 1.1 will also be performed.

3.2.1.4. Duration of Soft Tissue Response

Duration of soft tissue response per RECIST 1.1 in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of the first soft tissue response to the first documented objective evidence of progression (in soft tissue per RECIST 1.1 or in bone per PCWG3 guidelines) or start of new antineoplastic therapy. Those patients who did not have a soft tissue response will be excluded from the analysis. Censoring rules will follow those outlined for rPFS. The primary

evaluation of the duration of soft tissue response will be based on BICR overall tumor assessment. An evaluation based on derived investigator assessment using RECIST 1.1 will also be performed.

3.2.1.5. Proportion of Patients with PSA response

Proportion of patients with PSA response ≥50% in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the proportion of patients who have a decline from baseline in PSA (ng/mL) by at least 50%. A PSA response must be confirmed by a second consecutive value at least 3 weeks later.

3.2.1.6. Time to PSA Progression

Time to PSA progression in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of randomization to the date of the first PSA progression. PSA progression is defined as a ≥ 25% increase in PSA with an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline), confirmed by a second consecutive PSA value at least 3 weeks later. CCI [redacted]

3.2.1.7. Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of randomization to the first date cytotoxic chemotherapy is administered. Patients without initiation of cytotoxic chemotherapy will be censored at the date of last contact.

3.2.1.8. Time to Initiation of Antineoplastic Therapy

Time to initiation of antineoplastic therapy in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of randomization to the first date follow-up antineoplastic therapy is administered. Patients without initiation of antineoplastic therapy will be censored at the date of last contact.

3.2.1.9. Time to First Symptomatic Skeletal Event

Time to first symptomatic skeletal event in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of randomization to the date of the first symptomatic skeletal event. Patients without any symptomatic skeletal events will be censored at the date of last skeletal related event evaluation.

3.2.1.10. PFS2 Based on Investigator Assessment

PFS2 based on investigator assessment in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies: defined as the time from the date of randomization to the date of investigator documented disease progression (PSA progression, progression on imaging, or clinical progression) on the first subsequent

antineoplastic therapy for prostate cancer, or death from any cause, whichever occurs first.. For censoring rules see Section 6.2.2.9.

3.2.1.11. Time to Opiate Use for Prostate Cancer Pain

Time to opiate use for prostate cancer pain in patients with mCRPC unselected for DDR status and in patients with mCPRC harboring DDR deficiencies: defined as the time from the date of randomization to the first date of opiates used to treat cancer pain and will be based on the start date of medications reported on the concomitant medication page of the case report form (CRF) reported with a category of 'Opioids'. Patients without opiate usage will be censored at the date of last dose of study treatment.

3.2.2. PK Endpoints

PK characterized by predose trough and postdose plasma concentrations of talazoparib and enzalutamide and its N-desmethyl metabolite.

3.2.3. PD Endpoints

- **Proportion of patients with conversion from 5 or more CTCs per 7.5 mL at baseline to 4 or fewer CTCs per 7.5 mL postbaseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies**: patients with a CTC count < 5 per 7.5 mL of blood at baseline will not be analyzed for this conversion.

- **Proportion of patients with conversion from detectable CTCs per 7.5 ml at baseline to CTCs = 0 per 7.5 mL postbaseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies**: patients with a CTC count 0 per 7.5 mL of blood at baseline will not be analyzed for this conversion.

- **Proportion of patients with baseline CTC counts <5 who show increased CTC counts postbaseline, in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies**: patients with a CTC count ≥ 5 per 7.5 mL of blood at baseline will not be analyzed for this conversion.

- **Molecular profiling of tumor tissue remaining after genomic testing for eligibility during prescreening/screening, of saliva, and ctDNA; circulating protein biomarker profiles.**

- **Concordance of DDR deficiency results between the blood and tumor tissue based tests.**

3.2.4. PRO Endpoints

PROs in patients with mCRPC unselected for DDR status and in patients with mCRPC harboring DDR deficiencies:

- **Change from baseline in patient-reported pain symptoms per Brief Pain Inventory-Short Form (BPI-SF);**

- **Change from baseline in patient-reported general health status per European Quality of Life 5-dimension, 5-level scale (EQ-5D-5L);**

- **Change from baseline in patient-reported cancer-specific global health status/QoL, functioning, and symptoms per European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Cancer Questionaire (QLQ-C30);**

- **Change from baseline in patient-reported disease-specific functioning and symptom scales per EORTC QLQ-PR25**

- **Time to deterioration in patient-reported pain symptoms per BPI-SF** 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 randomization to onset of pain progression, where pain progression is defined as a 2-point or more increase from baseline for 2 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.

- **Time to definitive deterioration in patientreported- global health status/QoL per EORTC QLQ-C30**: defined as the time from the date of randomization to the date of the first definitive deterioration defined as a $\geq$ 10-point decrease from baseline and no subsequent observations of a < 10-point decrease from baseline. Patients without a definitive deterioration at the time of analysis will be censored at the date of last EORTC QLQ-C30 assessment.

- **Time to definitive deterioration in patientreported -diseasespecific- urinary symptoms per EORTC QLQ-PR25**: defined as the time from the date of randomization to the date of the first definitive deterioration defined as a $\geq$ 10-point increase from baseline and no subsequent observations of a < 10-point increase from baseline. Patients without a definitive deterioration at the time of analysis will be censored at the date of last EORTC QLQ-PR25 assessment.

3.3. Baseline Variables

For both Parts 1 and 2, the date of first dose (start date) of study treatment is the earliest date of non-zero dosing of either study drug. The date of last dose of study treatment is the latest date of non-zero dosing of either study drug. Talazoparib, placebo, and enzalutamide are all considered study drugs.

No windowing will be applied when defining baseline. Any deviations from the protocol specified window will be documented as protocol deviations.

For efficacy analyses and baseline characteristics associated with tumor assessments, the last assessment prior to randomization 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 (or prior to randomization for patients randomized but not dosed) will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

3.3.1. Stratification

Randomization is stratified by the following factors:

- Previous treatment with any novel hormonal therapy (NHT) or taxane-based chemotherapy (yes/no);
- DDR mutational status (deficient vs. non-deficient/unknown).
    - In the case of a test failure due to not meeting specified quality control metrics, or insufficient or inadequate blood or tumor tissue sample, the patient DDR mutational status will be considered unknown.
    - If results from blood and tumor tissue samples are both available prior to randomization, a positive result from either will be considered DDR-deficient.

The stratification factors will be specified by the investigator and recorded in the Interactive Web Response System (IWRS) before randomization. The stratified analysis of the primary efficacy endpoint will be based on the stratification information recorded in IWRS.

A secondary stratified analysis based on DDR mutational status derived from clinical database will also be performed. Especially because DDR status in IWRS cannot separate non-deficient and unknown status, derived DDR status from clinical database will be used to identify the non-deficient subpopulation.

3.4. Safety Endpoints

Incidence of adverse events characterized by type, severity (graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03), timing, seriousness and relationship to study treatment.

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified. On-treatment (treatment-emergent) is defined as the period between the first dose of any study treatment to 28 days after the last dose of the last study treatment discontinued, or before new antineoplastic therapy, whichever occurs first. In this study, talazoparib, placebo and enzalutamide are all considered study treatments. New antineoplastic therapies include cytotoxic chemotherapy, hormonal chemotherapy, and investigational agents for the treatment of prostate cancer. They will be identified based on a clinical review of all follow-up cancer therapies reported on the follow-up therapy CRF page.

3.4.1. Adverse Events

Adverse events (AE) 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 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 that occur on the same day as the first dose of study treatment will be considered baseline assessments.

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)

AESIs for talazoparib include the following:

- Acute Myeloid Leukemia (AML) (CQ)
- Myelodysplastic Syndromes (MDS) (SMQ)
- Second primary malignancies excluding nonmelanoma skin cancer (CQ)
- Pneumonitis (CQ)
- Embolic and thrombotic events, venous (SMQ).

The following AESIs for enzalutamide will be summarized as cluster terms:

- ALT > 3x ULN or AST > 3x ULN and Total Bilirubin ≥ 2x ULN
- Convulsions (seizure)
- Hypertension
- Neutrophil count decreased
- Cognitive and memory impairment
- Ischemic heart disease (IHD)
- Posterior reversible encephalopathy syndrome (PRES)
- Second primary malignancies
- Fall

- Fracture
- Loss of consciousness
- Severe cutaneous adverse reactions (SCAR)

The definition of each AESI is provided in Appendix 3.

3.4.2. Laboratory Data

Hematology and chemistry results will be programmatically graded according to the NCI CTCAE version 4.03 for relevant parameters. A shift summary of baseline grade by maximum postbaseline grade will be presented. Parameters that cannot be graded will be summarized relative to the normal range (i.e. normal range high or normal range low). Additional details are provided in Section 6.5.4.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data from Part 1 and Part 2 will be summarized separately.

4.1. Part 1 Analysis Sets/Populations

Analysis Set	Population	Applicable Analysis
Safety Population	All patients who received at least one dose of study treatment (talazoparib or enzalutamide).	• Safety analyses • Select baseline characteristics summaries
Pharmacokinetic Population	All patients who received at least one dose of study treatment in Part 1 and provided an evaluable PK sample.	• PK analyses
CTC Evaluable Population	All patients from the Safety Analysis Set Part 1 with a baseline CTCs assessment and at least 1 postbaseline CTCs assessment.	• CTC analyses

4.2. Part 2 Analysis Sets/Populations

All-comers Population: Analyses on the all-comers population will include patients unselected for DDR status enrolled in Cohort 1.

DDR-deficient population: Analysis on the DDR-deficient population will include patients with DDR deficiencies enrolled in Cohorts 1 and 2.

The following populations will be used in the data analyses.

Analysis Set	Population	Applicable Analysis

Intent-to-Treat Population	All patients randomized to double-blind study treatment in Part 2 regardless of whether or not treatment was administered.	• Efficacy analyses • Select baseline characteristics summaries
Safety Population	All patients who received at least one dose of study treatment (talazoparib/placebo or enzalutamide) in Part 2 and is based on the actual treatment received.	• Safety analyses • Select baseline characteristics summaries
Patient-Reported Outcome Population	A subset of ITT patients in Part 2 who completed the baseline and at least one postbaseline PRO assessment prior to the end of study.	• PRO analyses
Pharmacokinetic Population	All patients who received at least one dose of study treatment in Part 2 and provided an evaluable PK sample.	• PK analyses
CTC Evaluable Population	All patients from the Safety Analysis Set Part 2 with a baseline CTCs assessment and at least 1 postbaseline CTCs assessment.	• CTC analyses

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary objective of Part 1 was to determine the starting dose of talazoparib when given in combination with enzalutamide during Part 2. The initial analysis to evaluate the safety and PK of talazoparib in combination with enzalutamide will be performed after at least 12 patients receive the study treatment for at least 4 weeks in Part 1 (or sooner if warranted) to determine the appropriate dose level for the combination therapy.

The sample size of at least 12 for Part 1 is based on feasibility considerations and is expected to be adequate for determining the starting dose.

CCI [redacted]

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[redacted]

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Initially approximately 750 patients will be enrolled regardless of DDR mutation status (Cohort 1). Once enrollment is complete in the all-comers population, additional patients with DDR deficient disease will be enrolled (Cohort 2) until there are approximately 380 patients with DDR-deficient mCRPC across Cohorts 1 and 2. Analysis on the DDR-deficient population will include patients with DDR-deficient mCRPC enrolled in Cohorts 1 and 2.

CCI

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[redacted]

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5.2. General Methods

The conventions within this section apply to both Parts 1 and 2 unless otherwise specified.

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 randomized/treated at each center.

5.2.2. Nominal Timepoints

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal time point (i.e. assessment will not be slotted).

5.2.3. Definition of Study Day

The study day for assessments occurring on or after the first dose of study treatment (e.g., adverse event onset, tumor measurement) 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 (e.g., baseline characteristics, medical history) 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 (i.e. imputed dates will not be used in the derivation) among the following:

- All patient assessment dates (e.g. 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;
- Randomization date; 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. Assessment of the Impact of COVID-19 Pandemic

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 if necessary to further evaluate the outcome of the trial. Details of these summaries and analyses are included in the respective sections.

- A listing of protocol deviations related to COVID-19
- COVID-19 related AEs and deaths

5.2.6. COVID-19 Anchor Date

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

- For global pandemic reference date: use the date the World Health Organization designated COVID-19 as a global pandemic - March 11, 2020
- For China reference date: use the date COVID-19 was identified as the causative agent of outbreak in Wuhan by the China Center for Disease Control and Prevention - January 9, 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.

5.2.7. DDR Mutational Status

A patient will be considered DDR-deficient if they have at least one mutation in one of the following genes upon analysis with the FoundationOne CDx and/or FoundationOne CDx Liquid tests. Historical results reported on the CRF are allowed for analyses on tumor tissue only:

- ATM,

- ATR,
- BRCA1,
- BRCA2,
- CDK12,
- CHEK2,
- FANCA,
- MLH1,
- MRE11A,
- NBN,
- PALB2, or
- RAD51C.

The following definitions of DDR mutational status will be used in the subgroup analyses.

Table 3. DDR Subgroups

Primary DDR Subgroups	**DDR Definition**
1. IWRS	DDR-deficient vs. non-deficient/unknown. Based on IWRS randomization stratification.
2. Prospective tumor tissue and blood	DDR-deficient vs. non-deficient vs. unknown. Derived based on prospective tumor tissue-based results (results known prior to randomization) and prospective blood-based ctDNA results (results known prior to randomization). If prospective results from blood and tumor tissue samples are both available, a positive result from either will be considered prospectively DDR-deficient.
Exploratory DDR Subgroups	**DDR Definition**
3. Prospective plus retrospective plasma	DDR-deficient vs. non-deficient vs. unknown. Derived based on prospective tumor tissue-based results and prospective blood-based ctDNA results and retrospectively analyzed screening plasma-based ctDNA results known after randomization. Retrospectively analyzed plasma sample ctDNA results will only be incorporated for patients with an unknown DDR status by analysis #2.
4. Prospective plus retrospective plasma plus saliva	DDR-deficient vs. non-deficient vs. unknown. Derived based on prospective tumor tissue-based results and prospective blood-based ctDNA results and retrospectively analyzed screening plasma-based ctDNA results known after randomization and saliva samples. Retrospectively analyzed saliva results will only be used for patients with an unknown DDR status by analysis #3.
5. Tumor tissue	DDR-deficient vs. non-deficient vs. unknown. Derived based on tumor tissue-based results only.
6. ctDNA	DDR-deficient vs. non-deficient vs. unknown. Derived based on blood-based results only: Prospective ctDNA based on blood results; Retrospective ctDNA based on retrospectively analyzed screening plasma samples.

Table 3. DDR Subgroups

	For cohort 1, only retrospective ctDNA will be used, given that a majority of the patients did not have prospective ctDNA results.

5.2.8. Measurable Soft Tissue 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 CT or MRI
- Lymph nodes with short axis ≥ 15 mm when assessed by CT or MRI.

5.2.9. Tumor Assessment Date

For BICR, the tumor assessment date is the date of soft tissue or bone assessment at each nominal time point as provided in the BICR data.

For the investigator, the date of soft tissue assessment is the date provided by the investigator on the IOTA CRF and the date of the bone assessment is the date of bone scan on the Bone Scan Assessment CRF.

5.2.10. 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 randomization,
- 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),
- A bone scan must have been performed to assess bone lesions.

5.2.11. Adequate Post Baseline Tumor Assessment

For purposes of censoring in applicable time to event analyses (e.g. rPFS) an adequate assessment is defined as follows for BICR:

- An assessment where either the soft tissue response is progressive disease (PD) or
- An assessment where bone disease is assessed as PD or

- An assessment where the overall soft tissue response is CR, PR Stable Disease (SD), non-CR/non-PD (NN), or no disease (ND) AND a bone scan assessment has been performed within +/- 14 days with a value of ND or Non-PD.

For purposes of censoring in applicable time to event analyses (e.g. rPFS) an adequate assessment is defined as follows for investigator assessments (note the bone disease assessment is programmatically derived based on PCWG3 criteria utilizing questions on the bone scan assessment CRF page):

- An assessment were either the soft tissue response is progressive disease (PD) or
- An assessment where the derived bone disease assessment is PD or
- An assessment where the overall soft tissue response is CR, PR Stable Disease (SD), non-CR/non-PD (NN), or no evidence of disease (NED) AND a bone scan assessment has been performed within +/- 14 days with a value of ND or Non-PD.

5.2.12. 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 results for safety and PRO analyses. Additionally, unscheduled assessments will be used for efficacy analyses (e.g. deriving date of progression/censoring, best overall response, date of last contact).

5.2.13. Analyses for Continuous Endpoints

Descriptive statistics, including the number of observations (N), mean, standard deviation, median, minimum, and maximum values, will be provided for continuous variables.

5.2.14. Analyses for Categorical Endpoints

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.

5.2.15. Analyses for Longitudinal Data

A longitudinal mixed effect model will be use for the analysis of data measured repeatedly over time. CCI [redacted]

5.2.16. Analyses for Time-to-Event Endpoints

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. CCI [redacted] Summaries of the number and percentages of patients with an event will also be provided on summary tables and figures.

CCI [redacted]

5.3. Methods to Manage Missing Data

Missing data will not be imputed unless specified elsewhere in the SAP.

CCI [redacted]

5.3.1. Missing Dates

Date of Birth

A partial date of birth will be imputed as follows:

- If the year component is available with missing month and day, then impute the date of birth to 01 January of the year,
- If year and month are available with missing day, then impute the date of birth to the first day of the month.

If all date components are missing, then no date of birth will be imputed.

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 purposes of the analysis; 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

If the patient has known to have died but there is amissing or partial death date, the death date 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; 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 Follow-up Cancer Therapy

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

- The end date of new anticancer therapy will be included in the imputations for start date of new anticancer therapy. If the end date of new anticancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy

- partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anticancer therapy

- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.

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

  - 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.

Adverse Events:

Imputations for missing and partial adverse event dates will follow the Pfizer programming standards.

6. ANALYSES AND SUMMARIES

Overview of analysis presentation:

- Continuous data will be summarized using descriptive statistics (mean, median, SD, minimum, maximum, and 2-sided 95% CI)

- Categorical data (including point estimates) will be summarized by frequency counts, percentages and binomial 95% CIs using the Clopper-Pearson method.

- Kaplan-Meier estimates (time-to-event distirbutions) will be presented and displayed graphically where appropriate, together with a summary of associated statistics (including HRs, 2-sided 95% CIs, and 1-sided p-values).

- There will be no adjustment for multiplicity.

6.1. Part 1 Analyses

6.1.1. Primary Endpoint

Target safety events specified in Table 4 will be evaluated in the Part 1 safety analysis set.

Table 4. Target Safety Events: Part 1 (Open-Label Treatment)

Hematologic Toxicity
Any of the following considered possibly or probably related to talazoparib:
• Grade 4 anemia • Grade 4 thrombocytopenia • Grade 4 neutropenia (ANC <500/μL or <0.5 × 10^9/L) • Grade 3 thrombocytopenia associated with clinically significant bleeding • Grade 3 neutropenia or Grade 3 thrombocytopenia if daily dosing is interrupted for ≥7 days • Febrile neutropenia, defined as ANC <1000/μL with a single temperature of >38.3°C (>101°F) or a temperature of >38°C (100.4°F) sustained over a 1-hour period • Neutropenic infection (ANC <1000/μL or <1.0 × 10^9/L)
Nonhematologic Toxicity
Any Grade ≥3 adverse event considered possibly or probably related to talazoparib excluding the following:
• Grade ≥3 laboratory abnormalities not considered clinically significant • Grade ≥3 adverse event not considered clinically significant • Grade ≥3 nausea or vomiting that responds to medical intervention within 72 hours • Grade ≥3 diarrhea that can be medically managed to Grade ≤2 within 72 hours • Grade ≥3 fatigue that improves to Grade ≤2 within 7 days
Liver Toxicity
Any of the following considered possibly or probably related to talazoparib:
• ALT or AST >3 × ULN if baseline ALT or AST ≤3 × ULN • ALT or AST >5 × ULN (a lower threshold should be considered if the ALT or AST abnormalities are accompanied by symptoms and signs of hepatitis) AND 2-fold increases above baseline • ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN • Total bilirubin >5 × ULN

Toxicities will be classified by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

As the targeted safety events defined above include some subjective criteria or multiple criteria occurring simultaneously, an assessment of whether or not event met the criteria of being target safety events requiring a reduction in the starting dose for Part 2 will be made based on a review of individual patient data, summaries of all AEs, and exposure.

6.1.2. Secondary Endpoints [Pharmacokinetics]

A record-level dataset **Pharmacokinetic Analysis Set - Talazoparib** will include all talazoparib PK concentrations that meet the criteria below:

- PK samples collected at Week 1
- PK samples collected at Weeks 5, 9, 13, and 17 at the same dose level without any dose modification for at least 14 days.

Another record-level dataset **Pharmacokinetic Analysis Set - Enzalutamide** will include all enzalutamide concentrations that meet the criteria below:

- PK samples collected at Week 1
- PK samples collected at Weeks 5, 9, 13, and 17 for patients who did not experience any dose reductions or interruptions of enzalutamide.

Pharmacokinetic Analysis Set – Talazoparib and Pharmacokinetic Analysis Set – Enzalutamide will be used for PK parameter derivation and summary tables.

6.1.2.1. PK Concentrations

In Part 1, analyses of PK concentrations will include sampling at predose, 1, 2, 4, 6 and 24 hours postdose at Day 1 (week 1) and week 9. Additionally, blood samples for PK are collected at predose and 2 hours postdose at week 5 and predose at weeks 13 and 17.

All planned individual patients' plasma concentration data will be listed (Pharmacokinetic Population). PK samples obtained beyond 10% of the planned time will be included in the listings and could be included in the calculation of PK parameters (based on discretion of the pharmacokineticist), however, will be removed from figures and tables reporting mean concentrations per planned sampling times. Predose PK sample collection should occur prior to administration of the investigational product on that day, otherwise will be excluded. In all data presentations (except listings), values below the limit of the assay quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

Summary statistics will be provided for plasma concentrations of talazoparib and enzalutamide and its N-desmethyl metabolite at scheduled visits by time point (using the PK Analysis Sets for talazoparib or enzalutamide, see Section 6.1.2). Plasma concentration values below the limit of quantitation will be treated as zero in the descriptive statistics calculations. Zero concentrations will be considered as missing in geometric mean calculations. Spaghetti plots of individual concentrations against actual time postdose (separate plots for each dose and scheduled visit) will be presented.

6.1.2.2. PK Parameters

In estimating the PK parameters, BLQ values at the beginning of the profile will be set to zero. BLQ values that occur after the first quantifiable point will be set to zero. Values that

are embedded between BLQs, or quantifiable values occurring after two or more BLQs, may be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter. As appropriate, additional PK parameters may be calculated and reported.

The following PK parameters of talazoparib and enzalutamide and its Ndesmethyl metabolite will be summarized using the Pharmacokinetic Population (specifically using the record-level sets called PK analysis set – Talazoparib and PK analysis set – enzalutamide) as appropriate:

C_{max}, C_{trough}, T_{max}, AUC_{τ}, and CL_{ss}/F will be summarized by dose and study visit.

Dose-normalized AUC_{τ}, C_{max}, and C_{trough} will be summarized by study visit.

The above mentioned PK parameters (T_{max} excluded) will be summarized by arithmetic mean, standard deviation and CV, geometric mean, geometric CV, minimum, median, maximum value and the number of evaluable parameters. The PK characteristics of T_{max} will be described utilizing the number of observations, minimum, maximum and median. Geometric CV% is defined as sqrt(exp(variance of log transformed data)-1)*100

In addition, box and whisker plots for individual patient parameters AUC_{τ}, C_{max}, and C_{trough} by dose and scheduled visit as well as for dose-normalized AUC_{τ}, C_{max}, and C_{trough} by scheduled visit maybe be presented and overlaid with geometric means.

For all presentations, PK data from Part 1 and Part 2 will be pooled. However, separate summaries of PK parameters including AUC_{τ}, C_{max}, and C_{trough} by dose level and scheduled visit in addition to summaries of dose-normalized AUC_{τ}, C_{max}, and C_{trough} by scheduled visit will be generated for patients in Part 1.

6.1.3. Exploratory Endpoints

For CTC counts, a summary of the mean (standard deviation), median, and range of baseline and postbaseline values will be provided for patients in Part 1 CTC evaluable population. In addition, the number and percentage of patients with CTC count ≥ 5 vs. < 5 and CTC count > 0 vs. $=0$ per 7.5 mL will be presented as well.

The analysis of CTC count conversion from 5 or more CTC per 7.5 mL at baseline to < 5 CTC per 7.5 mL post baseline will exclude patients with a CTC count < 5 per 7.5 mL at baseline. The proportion of patients with such a conversion will be calculated along with the two-sided 95% CI using Clopper-Pearson method (exact method for a binomial proportion).

The analysis of CTC count conversion from detectable at baseline to 0 postbaseline will exclude patients with a CTC count of 0 per 7.5 mL of blood at baseline. The proportion of patients with such a conversion will be calculated along with the two-sided 95% CI using Clopper-Pearson method.

The analysis of the proportion of patients with baseline CTCs <5 who show increased CTCs postbaseline will exclude patients with a CTC count of ≥ 5 per 7.5 mL of blood at baseline. The proportion of patients with such a conversion will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

A separate analysis plan will be provided to describe analyses of molecular profiling of tumor tissue remaining after genomic testing for eligibility and of saliva and ctDNA.

Although not specifically listed as exploratory objectives, analyses of efficacy including rPFS, ORR in patient with soft tissue measurable disease at baseline, PSA response, and time to PSA progression may be evaluated during the course of the study and will be reported at the time of the final analysis of rPFS in all-comers, if not sooner. Derivations will follow the same rules outlined in section 6.2 for Part 2. Summaries will be descriptive and not inferential. Specifically summaries of time to event endpoints will be limited to medians and rates at specific timepoints of interest. Summaries of response rates will include number and percentage. Summaries will be provided regardless of mutation status or starting dose. Mutation status (where available) and starting dose will be provided in data listings.

6.2. Part 2 Analyses

6.2.1. Primary Endpoint -- rPFS

The primary efficacy analysis will compare rPFS based on BICR between talazoparib in combination with enzalutamide vs. talazoparib-matching placebo in combination with enzalutamide, CCI [redacted] A secondary analysis of rPFS based on investigator assessment will also be performed.

rPFS is defined as the time from the date of randomization to first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1 or in bone (upon subsequent confirmation) per PCWG3 guidelines, or death due to any cause, whichever occurs first, and will be summarized in months using the following calculation:

rPFS (months) = [date of event/censoring – randomization date +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 for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to baseline bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at Week 17 Visit [2]	Persistence of at least 2 lesions seen at week 9 AND 2 or more new bone lesions on bone scan (compared to Week 9 scan)

Table 5. Criteria for Evidence of Radiographic Progression

Date Progression Detected (Visit) [1]	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	Not applicable
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 Required for bone lesions observed on bone scan [2]	Persistent of at least 2 of the lesions identified as new compared to week 9
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression	Not applicable

[1] Progression detected by bone scan at an unscheduled visit prior to week 13 will require confirmation at least 6 weeks later following the confirmation criteria outlined in the table for week 9. All other unscheduled assessments will follow the confirmation criteria for week 17.
[2] Confirmation must occur at the next available scan.

rPFS will be censored in the following scenarios:

1) The patient will be censored on the date of the last adequate tumor assessment on or before the data cutoff date if the patient does not have radiographic progression and does not die.

2) The patient will be censored on the date of last adequate tumor assessment prior to the start of new antineoplastic therapy, if the patient starts a new antineoplastic therapy prior to radiographic progression or death.

3) The patient will be censored on randomization date, if the patient does not have baseline or postbaseline tumor assessments.

4) The patient will be censored on the date of the last adequate tumor assessment without evidence of disease progression prior to missed tumor assessments, if the patient misses 2 or more scheduled tumor assessments immediately prior to radiographic progression or death.

For the purpose of rPFS censoring, a patient will be censored on the date of the last adequate tumor assessment prior to the start of new antineoplastic therapy if the patient starts a new antineoplastic therapy prior to radiographic progression or death. If a patient has a 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’ prior to radiographic progression or death, the patient will also be censored on the date of the last adequate tumor assessment before the radiotherapy or surgery.

Two or more missed assessments is defined as follows:

- If the last adequate tumor assessment prior to the event occurs on or before 70 days from randomization, more than 119 days from that assessment (two 8-week assessments plus a 7-day assessment window) to the event;

- If the last adequate tumor assessment prior to the event occurs after 70 days AND on or before 126 days from randomization, more than 147 days from that assessment (an 8-week assessment plus a 12-week assessment plus a 7-day assessment window) to the event;

- If the last adequate tumor assessment prior to the event occurs after 126 days from randomization, more than 175 days from that assessment (two 12-week assessments plus a 7-day assessment window) to the event.

If a patient meets more than one censoring criteria described above, the patient's rPFS value will be censored at the earliest censoring date.

The stratified analysis will be based on the following randomization stratification factors:

Previous treatment with any NHT or taxane-based chemotherapy for CSPC (yes vs. no);

DDR mutational status (deficient vs. non-deficient/unknown).

The primary stratified analysis will be based on the stratification information recorded in IWRS. A secondary stratified analysis based on DDR mutational status derived from clinical database will also be performed. Especially because DDR status in IWRS cannot separate non-deficient and unknown status, derived DDR status from clinical database will be used to identify the non-deficient subpopulation.

Prior to Protocol Amendment 6, DDR mutational status for randomization/stratification was obtained from tumor tissue (archival or fresh biopsies) or historical test results (prior tumor tissue analysis using FoundationOne test). Starting with Protocol Amendment 6, DDR mutational status for randomization stratification was derived from either tumor tissue (archival slides or fresh biopsies or historical test results) or peripheral blood (liquid biopsy) prior to randomization. If prospective results from blood and tumor tissue samples are both available, a positive result from either will be considered prospectively DDR-deficient for randomization stratification. Retrospectively analyzed screening plasma samples with results known after randomization and retrospectively analyzed saliva results will also be incorporated for patients with an unknown DDR status in exploratory analyses. For details see Section 5.2.7.

Kaplan-Meier curves will be used to estimate the time-to-event distributions. CCI [redacted]

CCI [redacted]

Frequency (number and percentage) of patients with each event type (progression [including types of progression – i.e. bone progression, soft tissue progression, bone and soft tissue progression] or death) and censoring reasons will be presented by treatment arm along with the overall event and censoring rates.

Reasons for censoring will be summarized according to the categories in Table 6. If a patient meets multiple definitions for censoring at the same visit, the list will be used to define the hierarchy.

Table 6. Censoring Reasons and Hierarchy for rPFS

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new antineoplastic therapy or select radiotherapy/surgery before event.	Start of new antineoplastic therapy
3	Event immediately after missing at least two consecutive assessments	Event after missing assessments
4	No event and withdrawal of consent date ≥ randomization date OR End of study (EOS) = patient refused further follow-up	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and EOS present OR disposition page for any EPOCH after screening says patient will not continue into any subsequent phase of the study and no adequate postbaseline tumor assessment	No adequate postbaseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

CCI [redacted]

An overview forest plot of rPFS based on BICR assessment by the following subgroups will be presented. A similar forest plot based on investigator assessment will also be provided.

- Age (<70/≥70)
- Geographic region (North America, European Union [EU]/Great Britain [GBR], Asia, rest of world [ROW])
- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0, 1)
- Total Gleason Score at Diagnosis (<8/≥8)
- Stage at diagnosis (M0/M1)

- Type of progression at study entry (PSA only, radiographic progression with or without PSA progression)
- Baseline PSA (< vs. ≥ overall median)
- Site of metastasis at study entry (bone only, soft tissue only, both bone and soft tissue, none)
- DDR status by IWRS (DDR-deficient, non-deficient/unknown)
- Prior Taxane or NHT by IWRS (yes/no)

6.2.1.1. Sensitivity Analyses

The following sensitivity analyses will be performed separately for the all-comers and DDR-deficient populations to explore the robustness of each primary analysis result. Some of these sensitivity analyses will be presented in the CSR, while the remaining will be presented in other summary documents, for example, Summary of Clinical Efficacy and Summary of Clinical Safety.

The sensitivity analyses will be performed following the methods described for the primary analysis with the modifications below:

- Radiographic PFS counting all progression and deaths as events regardless of missing assessments or timing of the event (i.e. not censoring due to the start of a new antineoplastic therapy prior to event or due to missed assessments) based on BICR and investigator assessments.
- Radiographic PFS counting study treatment discontinuation, start of a new antineoplastic therapy, and occurrence of a symptomatic skeletal event as additional events based on BICR and investigator assessments. Censoring will be similar to that described for the primary analysis, except for the following:
    - Radiographic progression, death, discontinuation of study treatment (both treatment components), start of a new anti-cancer therapy, and a symptomatic skeletal event will all be considered as events. rPFS will be calculated as the time interval from the date of randomization to the date of radiographic progression, death, discontinuation of study treatment (both treatment components), start of a new anti-cancer therapy, or a symptomatic skeletal event, whichever occurs first.
- Radiographic PFS by assigning the dates of censoring and events only at scheduled assessment dates based on BICR and investigator assessments:
    - If a radiographic progression occurs within 7-day window of its scheduled assessment time, it will be assigned the scheduled assessment date. If a radiographic progression occurs outside the 7-day window and between 2 scheduled assessments, the date of the later planned assessment will be

assigned as the radiographic progression date (e.g., if a radiographic progression occurs between weeks 25 and 37, it will be assigned to week 37).

- In the event of death, the event date will not be adjusted.

DDR-deficient patients enrolled in China in Cohort 1 will be included in the analysis of DDR-deficient patient population. A sensitivity analysis of DDR-deficient patients by excluding the DDR-deficient patients enrolled in China in Cohort 1 will also be performed.

In addition, to assess the impact of COVID-19, the following sensitivity analyses of rPFS may be performed if COVID-19 related death is reported in at least 10 patients in the study:

- Radiographic PFS based on BICR assessment and censoring
- deaths due to COVID-19.
- Radiographic PFS based on investigator assessment and censoring deaths due to COVID-19.

BICR vs Investigator assessment:

A separate summary of the BICR assessment versus investigator assessment will be provided for the all-comers population and for the DDR-deficient population. These will include numbers of concordant and discordant assessments as well as the number of cases where a PFS event was assessed at different time points by the BICR and investigator.

The following categories will be summarized by treatment arm for each population:

- Agreement on time and occurrence of rPFS event (within 28 days) (a1),
- Agreement on rPFS event but investigator event occurred later (by >28 days) (a2),
- Agreement on rPFS event but investigator event occurred earlier (by >28 days) (a3),
- Investigator assessment of rPFS event, patient censored in the BICR analysis (b),
- Patient censored in the investigator assessment analysis of rPFS, BICR assessment of rPFS event (c), and
- Agreement on non-occurrence of rPFS event (d).

A +/- 28 day window will be used to assess the agreement on timing and occurrence of an rPFS event.

Total Event Discrepancy Rate (b+c)/N, Early Discrepancy Rate (a3+b)/(a+b), Late Discrepancy Rate (a2+c)/(a2+a3+b+c); and Overall Discrepancy Rate (a2+a3+b+c)/N will be calculated where a=a1+a2+a3.

6.2.2. Secondary Endpoints

Each secondary endpoint will be analyzed separately for the all-comers population and for the DDR-deficient population.

6.2.2.1. Overall Survival

OS is defined as the time from randomization to the date of death due to any cause. Patients last known to be alive will be censored at the date of last contact.

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

CCI [redacted]

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 OS

Hierarchy	Condition	Censoring Reason
1	No event and withdrawal of consent date ≥ randomization date 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

Frequency (number and percentage) of patients with an event and censoring reasons will be presented by treatment arm as follows:

- Death
    - Death due to COVID-19
- Withdrawal of consent
- Lost to follow-up

- Ongoing and no death.

To assess the impact of COVID-19, the following sensitivity analyses of OS may be performed by applying the additional censoring rules if COVID-19 related death is reported in at least 10 patiets in the study:

- Censoring deaths due to COVID-19.

6.2.2.2. Objective Response per RECIST 1.1

ORR is defined as the proportion of patients with measurable soft tissue disease at baseline with a best overall confirmed soft tissue response of CR or PR according to RECIST 1.1. Soft tissue 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 PCWG3 criteria. Patients without documented CR or PR will be considered non-responders.

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 are first met is not PD, the derived soft tissue timepoint response incorporating bone assessments will be PD. This derived timepoint response will be used to determining the best overall response (BOR). An example is provided in Table 8.

Table 8. 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	Progression criteria met (PD)	PD
	Week 17	CR	Progression criteria confirmed	PD
2	Week 9	CR	Progression criteria met (Non-PD)	CR
	Week 17	CR	Progression criteria NOT confirmed	CR
3	Week 9	SD	Non PD	SD
	Week 17	PR	Progression criteria met (PD)	PD

Table 8. Incorporation of Bone Progression into Best Overall Response

Example Number	Timepoint	Soft Tissue Response	Bone Assessment	Overall Soft Tissue Response Considering Bone Progression (derived)
	Week 25	PR	Progression criteria confirmed	PD

Best overall response will be assessed on patients with measurable disease based on reported overall responses at different evaluation timepoints from the date of randomization until documented disease progression (in soft tissue per RECIST 1.1 or in bone per PCWG3 guidelines) or start of new antineoplastic therapy 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', according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart and documented before progression and start of new antineoplastic therapy
- PR = at least two determinations of PR or better (and not qualifying for a CR) at least 4 weeks apart and before progression and start of new antineoplastic
- 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) ≥ 8 weeks after date of randomization and before progression and the start of new antineoplastic therapy
- PD = progression ≤ 16 weeks after date of randomization and not qualifying for CR, PR or SD
- Not Evaluable (NE) = all other cases.

For investigator assessments, global deterioration of health status will not be considered as documented disease progression.

For patients with measurable soft tissue disease at baseline, objective response rate (ORR) will be summarized for the two treatment arms. The primary evaluation of ORR will be based on BICR overall tumor assessment. A secondary evaluation of ORR will be based on the investigator assessments using derived response based on RECIST 1.1.

The frequency (number and proportion) of patients with best overall response of CR, PR, SD, Progressive Disease (PD), and NE (not-evaluable) will be tabulated.

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

- No adequate baseline assessment
- Early death (defined as death prior to 8 weeks after date or randomization)
- No postbaseline assessments due to COVID-19, i.e. participants miss tumor assessment visits due to COVID-19 pandemic
- No postbaseline assessments due to other reasons
- All postbaseline assessments have overall response NE
- New antineoplastic therapy started before first postbaseline assessment
- SD of insufficient duration (< 8 weeks after date of randomization)
- PD too late (> 16 weeks after date of randomization)

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

CCI [redacted]

[redacted]

6.2.2.3. Duration of Soft Tissue Response

For patients with measurable soft tissue disease at baseline who have an objective response per RECIST 1.1, duration of soft tissue response (DoR) is defined as the time from the date of the first soft tissue response to the first documented objective evidence of progression (in soft tissue per RECIST 1.1 or in bone per PCWG3 guidelines) or start of new antineoplastic therapy. Those patients who did not have a soft tissue response will be excluded from the analysis. The censoring rules for duration of soft tissue response are as described for rPFS in Section 6.2.1.

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

CCI [redacted]

Duration of soft tissue response will be reported for both the all-comers population and the DDR-deficient population.

In addition, for each DDR mutation, DoR by treatment arm may also be explored if there are enough patients with the mutation.

6.2.2.4. Proportion of Patients with PSA response ≥ 50%

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 without a baseline and at least one post baseline PSA assessment will not be analyzed for this endpoint. Only assessments performed from the date of randomization until confirmed PSA progression or start of new anticancer treatment (defined as systemic anticancer 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) will also be summarized descriptively by visit.

PSA response will be reported for both the all-comers population and the DDR-deficient population.

6.2.2.5. Time to PSA Progression

PSA progression is defined as the time from the date of randomization to the date of the first PSA value demonstrating progression, which is subsequently confirmed. If a patient starts a new antineoplastic therapy prior to PSA progression, the patient will be censored on the date of last PSA assessment prior to the start of a new antineoplastic therapy. 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 randomization.

> PSA Progression (months) = [date of PSA progression or censoring – randomization date +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.

Early rises (before week 12) should be ignored in determining progression. As such, 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 week 12, which is confirmed by a second consecutive value at least 3 weeks later.

PSA progression will be analyzed using a one-sided stratified log-rank test. Kaplan-Meier estimates will be presented by treatment arm with the median and 95% CIs.

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

Time to PSA progression will be reported for both the all-comers population and the DDR-deficient population.

6.2.2.6. Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy is defined as the time from randomization to the first use of cytotoxic chemotherapy. Cytotoxic chemotherapy will be identified based on a clinical review of all follow-up cancer therapies reported on the follow-up therapy CRF page. This review will occur prior to data unblinding.

Results will be reported in months ([date of event or censoring – randomization])/30.4375. Patients not starting any cytotoxic chemotherapy will be censored at the date of last contact.

CCI [redacted]

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

Time to initiation of cytotoxic chemotherapy will be analyzed for both the all-comers population and the DDR-deficient population.

6.2.2.7. Time to Initiation of Antineoplastic Therapy

Time to initiation of antineoplastic therapy is defined as the time from randomization to the first use of antineoplastic therapy. Such therapies include cytotoxic chemotherapy, hormonal chemotherapy, and investigational agents for prostate cancer. They will be identified based on a clinical review of all follow-up cancer therapies reported on the follow-up therapy CRF page. This review will occur prior to data unblinding.

Results will be reported in months ([date of event or censoring – randomization])/30.4375. Patients not starting any antineoplastic therapy will be censored at the date of last contact.

CCI [redacted]

The results will be reported for both the all-comers population and the DDR-deficient population.

6.2.2.8. Time to First Symptomatic Skeletal Event

Time to the first symptomatic skeletal event is defined as the time from randomization to the date of the first symptomatic fracture, surgery to the bone, radiotherapy to the bone, or spinal cord compression as reported on the Skeletal Related Events CRF page. Patients without any symptomatic skeletal events will be censored at the date of the last skeletal event assessment. Analyses will be in months ([date of event or censoring – randomization])/30.4375.

CCI [redacted]

The results will be reported for both the all-comers population and the DDR-deficient population.

6.2.2.9. PFS2 Based on Investigator Assessment

PFS2 is defined as the time from randomization to investigator documented disease progression (PSA progression, progression on imaging, or clinical progression) on the first subsequent antineoplastic therapy for prostate cancer, or death from any cause, whichever occurs first.

PFS2 (months) = [date of event/censoring – date of randomization +1]/30.4375

A patient will be considered to have an event if:

- date of documented progression on the first subsequent antineoplastic therapy is provided on follow-up cancer therapy CRF page; or
- the patient dies.

CCI [redacted]

The censoring and event date options to be considered for PFS2 along with the corresponding censoring reason and its hierarchy are presented in Table 9. The frequency (number and percentage) of patients with an event and censoring reasons will be presented by treatment arm.

Table 9. Outcome, Event/Censoring Dates, and Reasons for Censoring for PFS2

Scenario	Date of event/censoring	Outcome/ Censoring reason/ Censoring hierarchy
No PD[a] and No Death	Date of last adequate tumor assessment[b] documenting no PD	Censored/ No PD by investigator/ 1
No PD[a] and Death	Date of death	Event (Death)
PD[a] date > NTX1[c] start date and no death	Start date of NTX1[c]	Censored/ Start of new anticancer treatment before PD/ 2
PD[a] date > NTX1[c] start date and death	Date of death	Event (Death)

Table 9. Outcome, Event/Censoring Dates, and Reasons for Censoring for PFS2

Scenario	Date of event/censoring	Outcome/ Censoring reason/ Censoring hierarchy
PD[a] date ≤ NTX1 [c] start date and documented progression on NTX1	Documented progression on NTX1	Event (Date of documented progression on NTX1)
PD[a] date ≤ NTX1 [c] start date and no documented progression on NTX1 and death	Date of death	Event (Death)
PD[a] date ≤ NTX1 [c] start date and no documented progression on NTX1 and no death and the patient withdrew consent for follow-up	Date of Last Contact	Censored/ Withdraw of consent/ 3
PD[a] date ≤ NTX1 [c] start date and no documented progression on NTX1 and no death and the patient is lost to follow-up	Date of Last Contact	Censored/ Lost to follow-up/4
PD[a] date ≤ NTX1 [c] start date and no documented progression on NTX1 and no death and no other conditions met	Date of Last Contact	Censored/ Ongoing without PFS2 event/ 5

a PD is the first PD while on study treatment by investigator assessment per RECIST v1.1 or per PCWG3, without considering any censoring rules.
b If there is no adequate postbaseline assessment, then the censoring date is the date of randomization. If the patient has initiated next-line anticancer treatment, the last adequate postbaseline assessment on or prior to start date of next line anticancer treatment will be considered.
c NTX1 is the first new anticancer regimen

The PFS2 results will be reported for both the all-comers population and the DDR-deficient population.

6.2.2.10. Time to Opiate use for Prostate Cancer Pain

Time to opiate use for prostate cancer pain is defined as the time from date of randomization to the date of the first or new opiate medications for prostate cancer pain started after randomization and will be based on the start date of medications reported on the concomitant medication page of the CRF reported with a category of 'Opioids'. Patients without any opiate use will be censored at the last dose of study treatment.

CCI [redacted]

The results will be reported for both the all-comers population and the DDR-deficient population.

6.2.3. PRO Endpoints

All of the PRO endpoints described below will be analyzed using the PRO analysis set.

PRO endpoints will be analyzed for both the all-comers population and the DDR-deficient population.

6.2.3.1. Time to Event Endpoints

Time to Deterioration in Patient-reported Pain Symptoms per BPI-SF

Patient-reported pain symptoms (per the Pain Log – BPI-SF Question 3) 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 Question 3 at each visit period (i.e. collectively 7 consecutive days prior to each study visit and during study visit) are required for the 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 the analysis of 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 worst 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 used. Analgesic use is scored according to WHO criteria: zero for no use, one for use of non-opiate analgesics (e.g., non-steroidal anti-inflammatory drugs, acetaminophen, antidepressants, and agents targeting neuropathic pain), two for use of weak opiates for moderate pain (e.g., codeine and tramadol), and three for strong opiates for severe pain (e.g., morphine and fentanyl).

Time to deterioration in patient-reported pain symptoms per BPI-SF is assessed using the average pain 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 randomization 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. If there is a decrease in WHO analgesic usage score, then it will not be considered as pain progression even if there is a ≥2 point increase from baseline in the question 3 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.

Time to Definitive Deterioration in Patient-reported Global Health Status/QoL per EORTC QLQ-C30

Time to definitive deterioration in patient-reported global health status/QoL per EORTC QLQ-C30 is defined as the time from randomization to the first definitive deterioration defined as a ≥ 10-point decrease from baseline and no subsequent observations of a < 10-point decrease from baseline. Patients without a definitive deterioration at the time of analysis will be censored at the date of last EORTC QLQ-C30 assessment.

CCI [redacted]

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

Time to Definitive Deterioration in Patient-reported Disease-specific Urinary Symptoms per EORTC QLQ-PR25

Time to definitive deterioration in patient-reported disease-specific urinary symptoms per EORTC QLQ-PR25 is defined as the time from randomization to the first definitive deterioration defined as a ≥ 10-point increase from baseline and no subsequent observations of a < 10 point increase from baseline. Patients without a definitive deterioration at the time of analysis will be censored at the date of last EORTC QLQ-PR25 assessment.

CCI [redacted]

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

6.2.3.2. Descriptive Summaries and Change from Baseline

BPI-SF

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.

QLQ-C30

Analysis of the QLQ-C30 will consist of descriptive statistics for each scale on means and changes from baseline, overall change from baseline using a longitudinal mixed effects model, time to definitive deterioration, and graphical displays of means and changes from baseline over time.

QLQ-PR25

Analysis of the QLQ-PR25 will consist of descriptive statistics for each scale on means and changes from baseline, overall change from baseline using a longitudinal mixed effects model, time to definitive deterioration, and graphical displays of means and changes from baseline over time.

6.2.4. PK

In Part 2, analyses of PK concentrations will include sampling at predose and 2 hours post-dose at Weeks 3, 5 and 9, and pre-dose at Weeks 13 and 17.

The PK analyses for Part 2 of the study will be similar to those for Part 1 of the study. For details see Section 6.1.2. Separate summaries of dose-normalized C_{trough} by scheduled visit for patients in Part 2 may also be generated.

6.2.5. Other Endpoints

6.2.5.1. CTC Conversion Rates

CTC endpoints will be analyzed separately for both the all-comers population and the DDR-deficient population.

For CTC counts, a summary of the mean (standard deviation), median, and range of baseline and postbaseline values will be provided for patients in the CTC evaluable set. In addition, the number and percentage of patients with CTC count ≥ 5 vs. < 5 and CTC count > 0 vs. =0 per 7.5 mL will be presented as well.

For the analysis of CTC count conversion from 5 or more CTC per 7.5 mL at baseline to < 5 CTC per 7.5 mL post baseline, those patients with a CTC count < 5 per 7.5 mL at baseline will be excluded for this conversion endpoint. The proportion of patients with a conversion will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

For the analysis of CTC count conversion from detectable at baseline to 0 postbaseline, those patients with a CTC count of 0 per 7.5 mL of blood at baseline will be excluded for this conversion endpoint. The proportion of patients with such a conversion will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

For the analysis of the proportion of patients with baseline CTCs <5 who show increased CTCs postbaseline, those patients with a CTC count of ≥ 5 per 7.5 mL of blood at baseline will be excluded from the analysis. The proportion of patients with such a conversion will be calculated along with the two-sided 95% CI using the Clopper-Pearson method.

The results will be analyzed for both the all-comers population and the DDR-deficient population.

6.2.5.2. Molecular Profiling

A separate analysis plan will be written to describe analyses of molecular profiling of tumor tissue remaining after genomic testing.

6.2.5.3. Concordance of DDR deficiency results

The concordance of DDR deficiency results (DDR-deficient/non-deficient/unknown) will be explored for the following assay methods:

- Prospective tissue-based tests vs. retrospectively analyzed screening blood-based tests
- Prospective blood-based tests vs. retrospectively analyzed screening blood-based tests

6.3. Subgroup Analyses

Subgroup analyses will be performed if there is a sufficient sample size. The determination of whether or not there is a sufficient sample size will be defined after enrollment is complete and prior to database release. As a general rule, analyses of safety will only be performed if

there are ≥ 20 patients within the defined subset and analyses of time to event endpoints will only be performed if there are at least 10 events on each treatment arm within the subgroup. Deviations from these analyses will be described in the clinical study report.

Some of the subgroup analyses will be presented in the CSR, while the remaining will be presented in other summary documents, for example, Summary of Clinical Efficacy and Summary of Clinical Safety.

Besides the subgroup analyses presented in the overview forest plots described in Section 6.2.1, the following additional subgroup analyses will be performed for rPFS by BICR where the subgroups are subsets of the all-comers population:

- DDR mutational status derived using prospective/retrospective data (subgroup definitions 2-6 in Section 5.2.7).
- Renal impairment (moderate, mild, normal)
- Race (Asian, White, African American, other)
- Prior NHT (yes, no)
- Prior docetaxel (yes, no)
- Baseline bone protecting agent (yes, no)
- Baseline LDH value (< vs. ≥ median)
- Baseline hemoglobin value (< vs. ≥ median)
- Baseline ALP value (< vs. ≥ median)
- Baseline CTC Count (<5, ≥ 5)
- Baseline CTC Count (0, >0)

Similar subgroup analyses will be performed for Cohort 2.

A subgroup analysis for OS will be performed at the time of the final OS analysis using the same subgroups specified above for rPFS.

Subgroup analyses of other efficacy parameters and subgroups analyses for Part 1 data are not planned.

Key safety outputs for Part 2 will be provided to explore the following subgroups:

- Renal impairment (moderate vs. mild vs. normal),
- Age (<70 vs. ≥ 70),
- Asian vs. non-Asian.

Normal, mild, and moderate renal impairment 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, where eGFR will be captured on the CRFs.

Key safety outputs for Part 1 will be provided by starting dose. Additionally adverse events listings will consider the dose at the time of the start of the event.

6.4. Baseline and Other Summaries

Unless otherwise specified, the following summaries will be provided separately for the safety analysis set of Part 1 and for the ITT all-comers and DDR-deficient populations in Part 2. For Part 1, select data may be listed instead of summarized.

6.4.1. Baseline Summaries

The following demographic and baseline disease characteristics will be summarized:

- Age (continuous and by groups: <65; 65-<75; >=75)
- Race
- Asian vs. non-Asian
- Weight
- Body Mass Index (BMI)
- Geographic region (North America, Europe, Asia, Rest of World)
- Renal impairment at baseline (Normal, Mild, Moderate),
    - normal, mild, and moderate are defined based on baseline 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,
- Histopathological classification
- Baseline serum PSA (ng/mL)
- Baseline use of a bone protecting agent (yes, no)
- Gleason score (low [2-4], medium [5-7], high [8-10])
- Gleason score (<=6, 3+4=7, 4+3=7, 8, 9-10, not reported)
- ECOG performance status
- TNM stage at diagnosis
- TNM stage at study entry
- Disease localization at screening:
    - Bone only
    - Soft tissue only
    - Both bone and soft tissue
    - None

- Distribution of disease at screening:
  - Bone (includes bone with soft tissue component)
  - Lymph Node
  - Visceral Disease (lung or liver)
  - Visceral disease (lung)
  - Visceral disease (liver)
  - Other Soft Tissue
- Number of bone metastases at screening: n (%)
  - 0
  - 1-4
  - 5-9
  - 10-20
  - >20
- Type of progression at study entry:
  - PSA progression only
  - Bone progression only
  - Soft tissue progression only
  - PSA+ bone or soft tissue
  - Bone+ PSA or soft tissue
  - PSA+bone+soft tissue
- Baseline pain score by BP-SF (0-1; 2-3; >3),
- Baseline CTC count
  - Continuous summary
  - Categorical summary (≥ 5 CTC per 7.5 mL of blood, <5 CTC per 7.5 mL of blood)
  - Categorical summary (>0 CTC per 7.5 mL of blood, 0 CTC per 7.5 mL of blood)
- Time from primary diagnosis to randomization in months (date of randomization – date of diagnosis)/30.4375
- Derived DDR mutational status (positive, negative, unknown) with specific mutations prior to randomization
- DDR mutational status (positive, negative, unknown) with specific mutations based on blood samples only
- DDR mutational status (positive, negative, unknown) with specific mutations based on tumor tissue samples only

The number of patients in the following categories at the time of randomization will be summarized:

- Prior NHT or Taxane and DDR-deficient
- Prior NHT or Taxane and non DDR-deficient/unknown
- No Prior NHT or Taxane and DDR-deficient
- No Prior NHT or Taxane and non DDR-deficient/unknown

A listing will be provided with the strata (defined above) at the time of randomization as well as based on CRF data with a flag to indicate cases where there are differences between the derived data and the IWRS data at the time of randomization.

6.4.2. Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's SOC and PT. 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 by the experimental treatment arm. Summaries will be provided for all patients in the ITT population.

6.4.3. Prior Anticancer Treatments

Prior anticancer treatments include systemic therapy, radiation, and surgery.

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

- Patients with at least one type of prior anticancer systemic treatment including androgen deprivation therapy;
- Patients with at least one prior anticancer surgery;
- Patients with at least one prior anticancer radiotherapy with "primary treatment" and "salvage" intent;
- Patients with any prior androgen deprivation therapy.

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

  - Number of prior anticancer therapy regimens (including androgen deprivation therapy): None / 1 / 2 / ≥3.

The prior anticancer drugs will be coded in the WHO Drug coding dictionary and will be summarized using the number and percentage of patients by preferred term. A patient will be counted only once for a given preferred term, even if he/she received the same medication at different times. The summary will be sorted on descending frequency in the talazoparib in

combination with enzalutamide arm. In case of equal frequency, alphabetical order will be used.

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

- Prostatectomy,
- TURP,
- Prostate Biopsy,
- Bilateral Orchiectomy,
- Pelvic Node Dissection,
- Ureteral Stent,
- Nephrostomy.

Specific details on all other surgeries and radiotherapy (primary treatment and salvage) will be provided in data listings.

6.4.4. Study Conduct and Patient Disposition

Discontinuations from study treatment due to adverse events will be identified as either related or not related to study treatment. If causality is missing the event will be considered related to treatment. If multiple events lead to study treatment discontinuation and at least one was considered related, discontinuation will be reported as related to study treatment.

COVID-19 Related Disposition

A listing of all patients affected by COVID-19 will be created. The listing will present subject number identifier by investigational site, and a description of COVID-19-related events including:

- All protocol deviations
- Related AEs if available
- Deaths

6.4.5. Protocol Deviations

Important protocol deviations will be compiled prior to database release and will be summarized by category (n(%)) using the safety population for Part 1 and the ITT population for Part 2. Categories will be assigned by the study team.

In addition, all protocol deviations related to COVID-19 will be presented in a separate listing.

6.4.6. Study Treatment Exposure

Exposure summaries will be presented using the safety analysis set for each part.

Part 1 patients had a starting talazoparib dose of either 1 mg/day or 0.5 mg/day in combination with enzalutamide 160 mg/day, depending on timing of enrollment. The Part 1 data will be presented separately by the starting talazoparib dose.

For part 2, the daily dose of talazoparib is 0.5 mg/day given orally in combination with enzalutamide 160 mg/day at approximately the same time each day for patients with normal/mild renal impairment. The starting talazoparib dose will be 0.35 mg/day in combination with enzalutamide 160 mg/day for patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2).

Separate summaries will be provided for talazoparib and enzalutamide and 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 actual number of days on the treatment.
- Dose intensity (mg/week): Dose intensity is defined as the cumulative dose divided by the treatment duration.
- Relative dose intensity (%): Relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %. The planned dose intensity will be 3.5 mg (0.5 mg per day for 7 days) for patients without moderate renal impairment and 2.45 mg (0.35 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 (1 / 2 / 3) will be summarized by treatment arm.

Reasons for dose reductions will also be summarized. There could be more than one reason if multiple dose reductions occur for the same patient, though each reason will be counted only once for each patient. Percentages will be calculated based on the total number of patients in safety analysis set.

An dosing interruption is defined a 0 mg dose administered. (Note: A dosing interruption is not considered a dose reduction). The number and percentage of patients with dosing interruptions and the corresponding reasons will be summarized by treatment arm. There could be more than one reason if multiple dosing interruption occur for the same patient,

though each reason will be counted only once for each patient. Percentages will be calculated based on the total number of patients in safety analysis set.

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.

A summary of duration (days) of dosing interruptions due to any AEs and for anemia only for each dosing interruption will be provided, where 'n' is the number of dosing interruptions. A patient can contribute multiple observations, one for each interruption.

A summary of the total duration (days) of dosing interruptions due to AEs for each patient will also be provided.

6.4.7. Concomitant Medications

Concomitant medications refer to all medications that started or were ongoing at the time of randomization , started after randomization and continued during the on-treatment period for up to 28 days after the last dose of all the study treatments 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 Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term in descending order of frequency for the talazoparib in combination with enzalutamide arm. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. A patient will be counted only once for a given drug name, even if he/she received the same medication multiple times.

Concomitant non-drug treatments refer to non-drug treatments (radiation and surgery) administered during the on-treatment period. Non-drug treatments will be coded in MedDRA and will be summarized by MedDRA SOC and PT in descending order of frequency on the talazoparib in combination with enzalutamide arm. Patients will be counted only once per PT even if he/she received the same treatment multiple times.

Concomitant medications and non-drug treatments will be summarized by treatment arm for the Part 1 and Part 2 safety populations. Concomitant medications in will be listed for Part 1 and Part 2.

6.4.8. Subsequent Anticancer Therapies/Procedures

Subsequent systemic anticancer therapies are defined as therapies collected on the 'Follow-up Cancer Therapy' CRF page. Subsequent anticancer procedures include procedures collected on 'Follow-up Radiation Therapy' marked as curative or salvage, and 'Follow-up 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 by treatment arm for the Part 2 ITT Population. Subsequent anticancer therapies and procedures will be listed for Part 1 and Part 2.

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

6.5. Safety Summaries and Analyses

Unless otherwise specified, summaries of AEs and other safety parameters will provided separately for Part 1 and Part 2 and will be based on the safety population. For Part 1 the data will be analyzed by the starting dose of talazoparib. For Part 2 as it is anticipated that follow-up for the primary endpoint in the DDR-deficient population will be ongoing (i.e. treatment assignment will still be blinded) at the time of the final analysis of rPFS in the all-comers population, summaries will initially be performed only for the all-comers population. At the time of the final rPFS analysis in the DDR-deficient population safety data will be summarized for the combined populations of all-comers and DDR-deficient patients in Part 2.

6.5.1. Adverse Events

All analyses will be based on treatment-emergent events unless otherwise specified. AEs not considered treatment-emergent will be flagged in data listings.

For Part 1 and Part 2 separately, a high-level summary of adverse events will include the number and percent of patients with:

- Any AE;
- Serious AE;
- CTCAE Grade 3-4 AEs;
- Grade 5 AEs;
- AEs leading to dose reductions of talazoparib/placebo;
- AEs leading to dose reductions of enzalutamide;
- AEs leading to dose reductions of both talazoparib/placebo and enzalutamide;
- AEs leading to dosing interruptions of talazoparib/placebo;
- AEs leading to dosing interruptions of enzalutamide;
- AEs leading to dosing interruptions of both talazoparib/placebo and enzalutamide;
- AEs leading to permanent discontinuation of talazoparib/placebo;
- AEs leading to permanent discontinuation of enzalutamide;
- AEs leading to permanent discontinuation of both talazoparib/placebo and enzalutamide.

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

Summaries SOC and PT by treatment arm in decreasing frequency will be provided for:

- Treatment-Emergent AEs (All Causality);

- Treatment-Emergent AEs by Maximum CTCAE Grade (All Causality);
- Treatment-emergent COVID-19 related AEs (all causality);
- Treatment-Emergent AEs (Treatment Related);
- Treatmen -Emergent AEs by Maximum CTCAE Grade (Treatment Related);
- Serious Treatment-Emergent AEs (All Causality);
- Serious Treatment-Emergent AEs (Treatment Related);

An AE 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 of AEs will be provided by decreasing frequency of PT (summaries will not include SOC) in the talazoparib plus enzalutamide arm for Part 2 only:

- Treatment-Emergent AEs (All Causality) in either treatment arm;
- Treatment-Emergent AEs (All Causality) by Preferred Term and Maximum CTCAE Grade;
- Treatment-Emergent AEs Leading to Dosing Interruptions of Talazoparib (All Causality);
- Treatment-Emergent AEs Leading to Dosing Interruptions of Enzalutamide (All Causality);
- Treatment-Emergent AEs Leading to Dosing Interruptions of Both Talazoparib and Enzalutamide (All Causality);
- Treatment Emergent AEs Leading to Dose Reductions of Talazoparib (All Causality);
- Treatment Emergent AEsLeading to Dose Reductions of Enzalutamide (All Causality);
- Treatment Emergent AEsLeading to Dose Reductions of Both Talazoparib and Enzalutamide (All Causality);
- Treatment Emergent AEs Leading to Permanent Withdraw of Talazoparib (All Causality);
- Treatment Emergent AEs Leading to Permanent Withdraw of Enzalutamide (All Causality);
- Treatment Emergent AEs Leading to Permanent Withdraw of Both Talazoparib and Enzalutamide (All Causality);
- Treatment Emergent AEs between DDR-deficient patients and non-deficient patients (All Causality);
- Treamtment emergent AE between normal/mild vesus moderate renal impareiment (All Causality)
- Serious Treatment Emergent AEs (All Causality);

- Serious Treatment Emergent AEs (Treatment related).

Each patient will be counted only once within each SOC and PT.

If a patient has events with missing and non-missing toxicity grades, the maximum non-missing grade will be displayed. Missing grade will only be displayed in the event that only one AE has been reported for a patient and the grade is missing.

Summaries of time to first Grade 3 or 4 event and time to first SAE will also be provided for the safety populations in Part 2. Patients without an event will be censored as follows:

- if the patient has discontinued from study treatment the patient will be censored 28 days after the last dose of study treatment, or before systemic anticancer therapy, whichever occurs first, and

- if the patient is still on study treatment at the time of analysis the patient will be censored at the last date of contact.

6.5.2. Adverse Events of Special Interest

See section 3.4.1 for a list of AEs of Special Interest.

For Talazoparib AESIs, 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 provided to show the incidence of the following cluster terms:

- ANEMIA: anaemia, decreased hemoglobin, decreased hematocrit, red blood cell count decreased

- NEUTROPENIA: neutropenia and decreased neutrophil count

- THROMBOCYTOPENIA: thrombocytopenia and platelet count decreased

- LEUKOPENIA: leukopenia or white blood cell count decreased

- LYMPHOPENIA: lymphopenia or lymphocyte count decreased

AESIs for enzalutamide will be summazried by medical event only, not by individual contributing PTs if applicable..

6.5.3. Deaths

The frequency (number and percentage) of patients in the safety population 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.

Date and cause of death will be provided in individual patient data listings with selected dosing information (study treatment received, date of first / last administration, dose, etc.).

In addition, if there are ≥ 10 deaths due to COVID-19, a separate death summary will be created for COVID-19 related deaths.

6.5.4. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units for reporting.

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

Baseline will be defined as the last assessment performed on or prior to date of the first dose of study treatment (or prior to randomization for randomized patients). 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 (e.g., >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. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (e.g. 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 (e.g. 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 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 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 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 laboratory 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 local laboratory results. Worst overall grade 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 CTCAE terms that can be derived using one of several laboratory tests, the maximum postbaseline grade for a given patient and 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 (e.g., > ULN and < Lower Limit of Normal (LLN)), then both abnormalities are counted. Summaries at scheduled 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.

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

- 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

- 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, i.e., 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 for different treatment arms, 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 postbaseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

6.5.5. Vital Signs

Systolic and diastolic blood pressure (mmHg), heart rate (bpm), and temperature (Celsius) will be summarized at baseline and at all subsequent scheduled time points. Changes from baseline value will be presented for all scheduled time points. All recorded vital sign data will be listed for Parts 1 and 2.

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 10.

Table 10. 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

Table 10. Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Criteria for Potentially Clinically Significant Abnormalities
Weight	>10% decrease from baseline

CCI

CCI

[redacted]

8. STATISTICAL ANALYSIS FOR CHINA COHORT

The purpose of enrolling additional patients in China is to support the registration of the indication in China. Based on the current registration requirements, at least 113 mCRPC patients from China need to be enrolled into the study.

Patients enrolled in China in Cohort 1 and in the China extension cohort will be pooled together to form the China cohort. Data from the China cohort will be analyzed separately per local regulatory requirement in China and reported in a separate document.

Randomization and its stratification factors will be the same as the all-comers cohort. The analysis of the China cohort will use the same statistical methods. The only difference is the timing of the analysis.

A subgroup analysis of the efficacy and safety of the patients enrolled in China and Asia in Cohort 1 will be performed at the time of the final rPFS analysis for the all-comers cohort if the all-comers cohort meets its primary endpoint. The subgroup analysis may form the basis for regulatory submission in China. Otherwise an analysis of all the patients enrolled in the China cohort will be performed when at least 50% rPFS events are observed in the China cohort.

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10. APPENDICES

Appendix 1. Summary of Key Efficacy Analyses

Endpoint	Analysis Type	Populations	Analysis Model
rPFS based on BICR	Primary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
OS	Secondary efficacy analysis (alpha protected)	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
ORR for patients with measurable soft tissue disease at baseline	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Cochran–Mantel–Haenszel test
Duration of soft tissue response	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Kaplan-Meier method
PSA response	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Cochran–Mantel–Haenszel test
Time to PSA progression	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
Time to initiation of cytotoxic chemotherapy	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
Time to initiation of antineoplastic therapy	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
Time to first symptomatic skeletal event	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
PFS2	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis
Time to opiate use for prostate cancer pain	Secondary efficacy analysis	All-comers and DDR-deficient, respectively	Stratified log-rank test; Cox proportional hazard analysis

Appendix 2. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline Phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AML	Acute Myeloid Leukemia
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BICR	blinded independent central review
BLQ	below the limit of quantitation
BPI-SF	Brief Pain Inventory-Short From
bpm	beats per minute
CI	confidence interval
C_{max}	maximum observed concentration
CR	complete response
CRF	case report form
CSPC	castration sensitive prostate cancer
CSR	clinical study report
CTCs	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DDR	DNA damage repair
DNA	deoxyribonucleic acid
ECOG	Easter Cooperative Oncology Group
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
E-DMC	external data monitoring committee
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-dimension, 5-level scale
ITT	intent-to-treat
IWRS	Interactive Web Response System
LLN	Lower limit of normal.
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic Syndrome
mCRPC	metastatic castration resistant prostate cancer
N/A	not applicable
NCI	National Cancer Institutes
ND	no disease
NED	no evidence of disease
NGS	next generation sequencing

Abbreviation	Term
NHT	novel hormonal therapy
NN	Non-CR/Non-PD
NTX1	first new anticancer regimen
ORR	Objective response rate
OS	overall survival
OTR	Out of toxicity range
PARP	Poly (adenosine diphosphate [ADP]-ribose) Polymerase
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PFS2	Progression free survival on next line therapy
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	preferred term
QoL	quality of life
QLQ-C30	Quality of Life Cancer Questionaire
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression free survival
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International d'unités
SOC	System Organ Class
TBILI	total bilirubin
Tmax	time to maximum observed concentration
ULN	Upper limit of normal
WHO	World Health Organization

Appendix 3. Definition of Adverse Events of Special Interests

AESIs for Talazoparib:

Event Grouping of Interest	Definition
Acute myeloid leukemia	Acute myeloid leukemia (AML) (CQ)
Myelodysplastic syndromes	Myelodysplastic syndromes (MDS) (SMQ)
Second primary malignancies	Second primary malignancies excluding nonmelanoma skin cancer (CQ)
Embolic and thrombotic events	Embolic and thrombotic events, venous (SMQ)
Pneumonitis	Pneumonitis (CQ)

AESIs for Enzalutamide:

Event Grouping of Interest	Definition
ALT > 3x ULN or AST > 3x ULN and Total Bilirubin ≥ 2x ULN	ALT > 3x ULN or AST > 3x ULN and Total Bilirubin ≥ 2x ULN
Convulsions (seizure)	Narrow SMQ of "Convulsions".
Hypertension	Narrow SMQ of "Hypertension".
Neutrophil count decreased	Preferred terms of 'Neutrophil count decreased', 'Neutropenia', 'Agranulocytosis',' Granulocyte count decreased', 'Granulocytopenia', 'Febrile neutropenia', 'Neutrophil percentage decreased', 'Band neutrophil count decreased', and 'Band neutrophil percentage decreased' 'Neutropenic sepsis', 'Neutropenic infection', 'Neutrophil count abnormal'
Cognitive and memory impairment	All preferred terms in MedDRA high-level group term (HLGT) "mental impairment disorders"
Ischemic heart disease (IHD)	Narrow SMQs of "myocardial infarction" and "other ischemic heart disease"
Posterior reversible encephalopathy syndrome (PRES)	Preferred term of posterior reversible encephalopathy syndrome

Event Grouping of Interest	Definition
Second primary malignancies	Narrow SMQs of "Malignant or unspecified tumours" customized to exclude preferred terms of "Congenital fibrosarcoma" , "Congenital malignant neoplasm" , "Congenital retinoblastoma" , ", "Metastases to…" , "Metastasis" , "Metastatic neoplasm" , "Prostate cancer…" , "Carcinoid tumour of the prostatec, and "Neoplasm prostate" AND (inclusive of) Narrow SMQ of "Myelodysplastic syndrome" AND (inclusive of) All preferred terms under HLT of "Myeloproliferative disorders (excl leukaemias)" Note: Non-melanoma skin cancers are excluded (preferred terms of "Basal cell carcinoma" , "Basosquamous carcinoma" , "Basosquamous carcinoma of skin" , "Keratoacanthoma" , "Skin cancer" , "Skin cancer metastatic" , "Squamous cell carcinoma" , "Squamous cell carcinoma of skin" , "Lip squamous cell carcinoma")
Fall	Preferred term of "Fall"
Fracture	All preferred terms under the MedDRA HLGT: "Fractures" , "Bone and Joint Injuries"
Loss of consciousness	Preferred terms of "Loss of consciousness" , "Syncope" , and "Presyncope"
Severe cutaneous adverse reactions (SCAR)	Narrow SMQ of "Severe cutaneous adverse reactions"

SMQ: standardized MedDRA query, HLT: high-level term, HLGT: high-level group term