CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Open-Label, Single-Arm Study of Pamiparib (BGB-290) for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Homologous Recombination Deficiency (HRD)
Protocol Identifier:	Pamiparib (BGB-290-202)
EudraCT Number:	2018-002587-28
Phase:	2
Protocol Version 0.0:	27 July 2018
Protocol Version 1.0:	16 October 2018
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2929 Campus Drive, Suite 300 San Mateo, California 94403 USA
Sponsor Medical Monitor:	[redacted]

FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Open-Label, Single-Arm Study of Pamiparib (BGB-290) for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Homologous Recombination Deficiency (HRD)

BeiGene Approval:

_____ _____

[redacted] Date

Sponsor Medical Monitor

SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.
Investigational Product:	Pamiparib (BGB-290) capsule
Title of Study:	A Phase 2, Open-Label, Single-Arm Study of Pamiparib (BGB-290) for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Homologous Recombination Deficiency (HRD)
Protocol No:	BGB-290-202
Number of Patients:	Approximately 100 patients
Study Centers:	Approximately 45 centers in Asia, Australia, Europe, and the United States
Study Phase:	2
Treatment Duration:	Patients will receive daily treatment during the study until occurrence of progressive disease (PD), unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Study Objectives:

Pamiparib, a potent and selective inhibitor of poly (ADP-ribose) polymerase (PARP)1 and PARP2, showed potent PARP-trapping activity and antiproliferative activity against several cell lines harboring BRCA gene mutations or other homologous recombination deficiencies (HRD).

Primary Objective:

- To evaluate the efficacy of pamiparib in patients with metastatic castration-resistant prostate cancer (mCRPC) positive for circulating tumor cells (CTC) with homologous recombination deficiency (CTC-HRD-positive; per Epic Sciences assay), as per Prostate Cancer Clinical Trials Working Group [PCWG3] criteria

Secondary Objectives:

- To further evaluate the efficacy of pamiparib in patients with CTC-HRD-positive mCRPC with measurable disease (Cohort 1 of Synopsis Table 1), as per PCWG3 criteria
- To further evaluate the efficacy of pamiparib in patients with CTC-HRD-positive mCRPC with or without measurable disease (Cohorts 1 and 2 of Synopsis Table 1, respectively), as per PCWG3 criteria
- To evaluate the safety and tolerability of pamiparib

Exploratory Objectives:

- [redacted]

Study Endpoints:

Assessments are per the investigator except when indicated otherwise. Assessments will be conducted in accordance with Good Clinical Practice and all applicable regulatory requirements.

Primary Endpoints:

- Objective response rate (ORR; defined as the proportion of patients with best objective response of complete response (CR) or partial response (PR) confirmed at a subsequent timepoint ≥ 4 weeks later) by Independent Review Committee (IRC) for CTC-HRD-positive patients with measurable disease (Cohort 1 of Synopsis Table 1)
- Prostate-specific antigen (PSA) response rate (defined as the proportion of patients with PSA decline ≥ 50% from baseline [confirmed by a second PSA value ≥ 3 weeks later]) for CTC-HRD-positive patients with or without measurable disease (Cohorts 1 and 2 of Synopsis Table 1, respectively)

Secondary Endpoints:

Patients with CTC-HRD-Positive mCRPC with Measurable Disease (Cohort 1 of Synopsis Table 1) per PCWG3 Criteria

- Duration of response (DOR) by IRC
- ORR by investigator
- Time to objective response
- Clinical benefit rate (defined as the proportion of patients with a documented confirmed CR, PR, or stable disease)

Patients with CTC-HRD-Positive mCRPC with or without Measurable Disease (Cohorts 1 and 2 of Synopsis Table 1, respectively) per PCWG3 Criteria

- Time to PSA response
- Duration of PSA response
- Time to PSA progression (defined as the time from the date of the first dose of study drug to a ≥ 25% increase in PSA with an absolute increase of ≥ 2 ng/mL above the nadir [or above the baseline for patients with no PSA decline after 12 weeks], confirmed by a second value ≥ 3 weeks later)
- Time to symptomatic skeletal event (SSE; defined as time from the date of the first dose of study drug to the first symptomatic fracture, radiation or surgery to bone, or spinal cord compression)
- Radiographic progression-free survival (rPFS; defined as the time from the date of the first dose of study drug to radiographic disease progression by IRC or death due to any cause, whichever

occurs first)

- Overall survival (OS)

All Patients (Cohorts 1, 2, 3, and 4 of Synopsis Table 1)

- Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 or higher

Exploratory Endpoints:

- [redacted]

Study Design:

This is an open-label, single-arm, global Phase 2 study to evaluate the efficacy and safety of single-agent poly (ADP-ribose) polymerase 1 and 2 (PARP1/2) inhibitor pamiparib in biomarker positive mCRPC patients. Biomarker positivity is defined as CTC-HRD-positive and/or deleterious germline or somatic mutation in BRCA1 or BRCA2.

To be eligible for the study, biomarker-positive patients must have progressed on or after at least one androgen receptor-targeted therapy for mCRPC (eg, enzalutamide, abiraterone acetate/prednisone, bicalutamide, flutamide, apalutamide, or nilutamide), received at least 1 taxane-based therapy for metastatic prostate cancer, and have PSA progression as per PCWG3 criteria at time of study entry. The primary endpoints are ORR by IRC for patients with measurable disease ($n \approx 50$) and PSA response rate for patients with or without measurable disease ($n \approx 80$) as per PCWG3 criteria.

Cohort 1 will include 50 mCRPC patients with CTC-HRD-positive, measurable metastatic disease (soft tissue with/without bone lesions), and positive BRCA1/2 mutation or negative/unknown BRCA1/2 mutation. Cohort 2 will include 30 mCRPC CTC-HRD positive patients with bone metastasis only and positive or negative/unknown BRCA1/2. Cohort 3 and 4 will include 20 mCRPC CTC-HRD negative/unknown patients with BRCA1/2 positive mutations, metastatic disease (measurable soft tissue with/without bone), and bone only (see Synopsis Table 1).

After enrollment, patients will receive pamiparib 60 mg orally twice a day in cycles of 28 days.

Safety assessments will occur on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and as needed. Dose modifications will be made if appropriate. Adverse events (AEs) will be followed and documented during the treatment phase and for approximately 30 days after the last dose of pamiparib or until

initiation of new anticancer therapy, whichever occurs first. AEs will be graded according to NCI-CTCAE Version 4.03 or higher. A Safety Monitoring Committee will periodically review safety data.

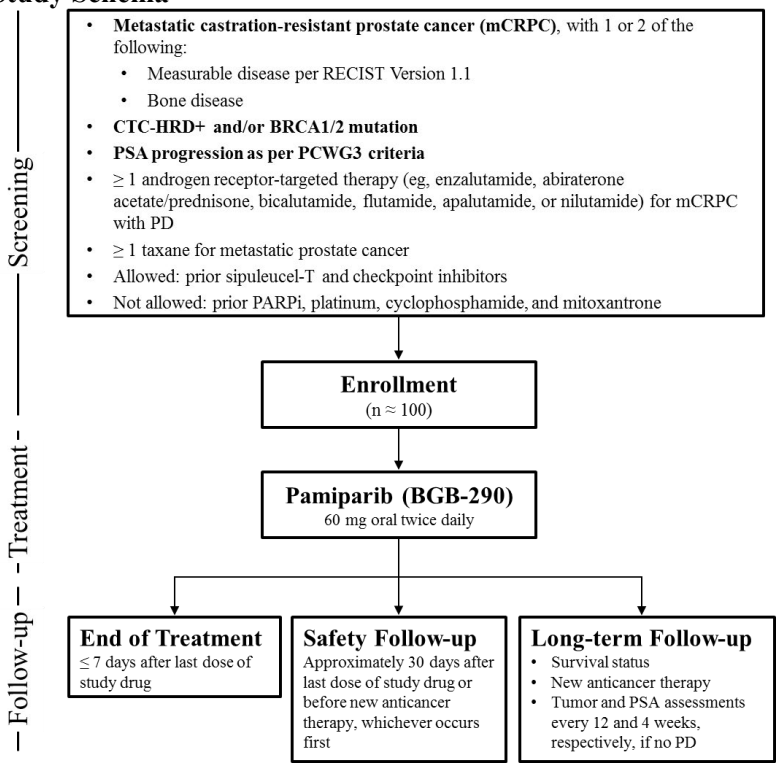
PK samples for pamiparib will be collected at various timepoints at all non-China centers and at centers with such capability in China. In addition, tumor tissue (if available) and blood samples will be obtained to explore biomarkers of pharmacodynamics, response, and resistance to pamiparib in mCRPC.

Disease status will be assessed by the investigator using PCWG3 criteria. Patients will undergo tumor assessments every 8 weeks (± 7 days) for 24 weeks, then every 12 weeks (± 7 days), or as clinically indicated. PSA assessments will occur at screening, on Day 1, and then every 4 weeks (± 7 days), or as clinically indicated.

Administration of pamiparib will continue until PD, unacceptable toxicity, death, or another discontinuation criterion is met. Once the treatment phase has been completed, an End-of-Treatment Visit should occur within 7 days of stopping pamiparib with subsequent phases of safety and long-term follow-up.

Long-term follow-up will include tumor and PSA assessments every 12 weeks and 4 weeks (± 7 days), respectively, for those patients without PD, survival status, and initiation of new anticancer therapy. Long-term follow-up will continue until the patient dies or another criterion for discontinuation from study is met.

Study Schema



Abbreviations: CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay; mCRPC, metastatic castration-resistant prostate cancer; PARPi, PARP inhibitor; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, progressive disease; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

Notes: Key assessments during the treatment phase: tumor assessments every 8 weeks (± 7 days) for 24 weeks, then every 12 weeks (± 7 days), or as clinically indicated; and patient-reported outcomes, PSA, adverse events, hematology, and chemistry every 4 weeks. Pamiparib is to be administered continuously.

Synopsis Table 1. Patient Cohorts

Cohort	1		2		3	4
Patients	n ≈ 50		n ≈ 30		n ≈ 20	
CTC-HRD	+		+		-/∅	
Metastatic disease	Measurable soft tissue ± bone		Bone only		Measurable soft tissue ± bone	Bone only
BRCA1/2 mutation	1A: +	1B: -/∅	2A: +	2B: -/∅	+	

Abbreviations: ∅, biomarker status unknown; CTC-HRD-, negative for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay; CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay.

Summary of Eligibility Criteria:

The population under study is men (≥ 18 years of age) with histologically or cytologically confirmed adenocarcinoma or poorly differentiated adenocarcinoma of the prostate without neuroendocrine differentiation with HRD deficiency by CTC-HRD assay and/or deleterious germline or somatic mutation in BRCA1 or BRCA2; mCRPC measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and/or bone disease. Patients must have PSA progression with ≥ 3 rising PSA levels with ≥ 1 week between determinations and a screening PSA ≥ 2 µg/L (2 ng/mL). Patients must be surgically or medically castrated with serum testosterone levels of ≤ 1.73 nmol/L (50 ng/dL), must have received ≥ 1 prior androgen receptor-targeted therapy, and must have received ≥1 taxane-based therapy.

Test product, dose, and mode of administration:	Pamiparib 60 mg orally twice a day
Reference therapy, dose, and mode of administration:	Not applicable

Dose Modifications:

Dosing of pamiparib can be withheld for up to 28 days consecutively. Dose reductions are allowed in 20 mg per dose decrements. A maximum of 2 dose reductions is allowed before the patient must be permanently withdrawn from pamiparib. If drug is planned to be held ≥ 28 days, the medical monitor must be contacted before permanent patient discontinuation from pamiparib.

Concomitant Therapy and Clinical Practice:

All treatments and supportive care, including antiemetic therapy, hematopoietic growth factors, and/or red blood cell/platelet transfusions, that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the local standards of medical care.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluid supplementation, taken by or administered to the patient within 28 days before Day 1 and 30 days after the last dose of pamiparib will be recorded.

Patients are not allowed to receive other anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, radionuclide therapy, immunotherapy, investigational agent, Chinese

anticancer medicine, or herbal remedies ≤ 5 half-lives if the half-life is known, ≤ 14 days if not known, before Day 1 and during the study. In addition, patients are not allowed to receive radiotherapy ≤ 21 days (≤ 14 days, if a single fraction of radiotherapy) before Day 1 and during the study. Bisphosphonate and denosumab use is permitted if the patient had already been receiving it at a stable dose ≥ 28 days before Day 1.

The primary metabolic pathway for pamiparib involves the cytochrome P450 (CYP)3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. In addition, careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Criteria for Evaluation:

Efficacy:

Following the screening tumor assessment, tumor assessments will occur at the schedule of every 8 weeks (± 7 days) after Day 1 for 24 weeks, then every 12 weeks (± 7 days). Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response and DOR will be assessed by the investigator using PCWG3 criteria. The same imaging method(s) used at screening must be used throughout the study. A documented standard-of-care tumor assessment may be used as the screening assessment provided it meets protocol requirements.

PSA levels will be collected and tested in a certified local laboratory during screening, on Day 1, and every 4 weeks (± 7 days), or as clinically indicated. In addition, at least, the 3 most recent PSA levels before Day 1 (≥ 1 week between determinations) must be provided to document PSA progression before study entry. Increases and decreases in PSA will be tracked to assess PSA responses as defined by the PCWG3 criteria. A PSA response or progression must be confirmed ≥ 3 weeks later.

Patients who do not have objective disease progression at the time of pamiparib permanent discontinuation but meet other discontinuation criteria will continue to have tumor and PSA assessments per protocol. Survival status of patients will be monitored through all phases of the study.

Safety:

Safety will be monitored throughout the study. Safety assessments include AE monitoring and reporting, physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory tests.

Statistical Methods:

Analysis Sets:

- Safety Analysis Set: includes all patients enrolled into the study who receive any dose of pamiparib. The Safety Analysis Set will be used for all safety analyses.
- Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1 of Synopsis Table 1): includes all patients in the Safety Analysis Set who had measurable disease at baseline and at least 1 postbaseline tumor assessment, unless they permanently discontinue pamiparib or the study early due to clinical progression or death before tumor assessment. The Efficacy-Evaluable Analysis Set is the primary analysis set for tumor response analysis.
- PSA-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2 of Synopsis Table 1): includes all patients in the Safety Analysis Set as per Inclusion Criterion 7 at baseline (≥ 3 rising PSA levels with ≥ 1 week between determinations and screening PSA ≥ 2 µg/L) and who had at least 1 postbaseline PSA measurement, unless they permanently discontinue pamiparib or the study early due to clinical progression or death before completed PSA

assessment.

- PK Analysis Set: includes all patients who received pamiparib and for whom valid pamiparib PK parameters can be estimated.

Efficacy Analyses:

Primary Efficacy Endpoint Analysis:

The primary endpoints of the study include ORR by IRC in CTC-HRD-positive patients with measurable disease and PSA response rate in CTC-HRD-positive patients with or without measurable disease per PCWG3 criteria.

ORR is defined as the proportion of patients with best objective response of CR or PR confirmed at a subsequent timepoint ≥ 4 weeks later by IRC assessment. Patients without tumor assessment are considered non-responders.

ORR is assumed as 35% for pamiparib and estimated as 15% for historical control in the study population. The null and alternative hypotheses are set as follows:

H_0 : ORR = 15%

H_a : ORR > 15%

PSA response rate is defined as the proportion of patients with PSA decline ≥ 50% from baseline (confirmed by a second PSA value ≥ 3 weeks later).

PSA response rate is assumed as 50% for pamiparib and estimated as 30% for historical control in the study population. The null and alternative hypotheses are set as follows:

H_0 : ORR = 30%

H_a : ORR > 30%

Binomial exact tests will be performed for above hypotheses in the Efficacy-Evaluable Analysis Set. Two-sided binomial exact 95% confidence interval (CI) of response rate will be constructed to assess the precision of the estimates.

To control the overall study type-I error rate, ORR and PSA response rate will be tested sequentially. If the ORR test shows significance at 1-sided 0.025 level, PSA response rate will be tested at a 1-sided 0.025 significance level.

The primary efficacy analyses will be conducted when mature response data have been observed, which will be determined by the sponsor.

A sensitivity analysis of response rate will be conducted using the Safety Analysis Set.

ORR and PSA response rate will be summarized in the specified subgroups: age group (< 65 versus ≥ 65), race, geographic region, Eastern Cooperative Oncology Group performance status, BRCA1/2-mutant status, and number of prior lines of therapy.

Secondary Efficacy Endpoint Analyses:

DOR by IRC assessment, ORR by investigator, and time to objective response and clinical benefit rate as assessed by investigator will be evaluated in patients with CTC-HRD-positive mCRPC with measurable disease per PCWG3 criteria.

Time to PSA response, duration of PSA response, time to PSA progression, time to SSE, rPFS by IRC, and OS will be evaluated in patients with CTC-HRD-positive mCRPC with or without measurable disease per PCWG3 criteria.

DOR is defined as the time from the date of the earliest documented confirmed response of CR or PR

to radiographic disease progression by IRC or death due to any cause, whichever occurs first.

Time to objective response is defined as the time from the date of the first dose of study drug to the first documented confirmed response of CR or PR.

Clinical benefit rate is defined as the proportion of patients with a documented confirmed response of CR, PR, or stable disease.

Time to PSA response is defined as the time from the date of the first dose of study drug to the first documented confirmed PSA response.

Duration of PSA response is defined as the time from the date of the earliest documented confirmed PSA response to PSA progression or death due to any cause, whichever occurs first.

Time to PSA progression is defined as the time from the date of the first dose of study drug to a ≥ 25% increase in PSA with an absolute increase of ≥ 2 µg/L above the nadir (or above the baseline for patients with no PSA decline after 12 weeks), confirmed by a second value ≥ 3 weeks later.

Time to SSE is defined as the time from the date of the first dose of study drug to the first symptomatic fracture, radiation or surgery to bone, or spinal cord compression.

rPFS is defined as the time from the date of the first dose of study drug to radiographic disease progression by IRC or death due to any cause, whichever occurs first.

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

Time-to-event variables of DOR, duration of PSA response, time to PSA progression, time to SSE, rPFS, and OS will be estimated using the Kaplan-Meier method. Median of these time-to-event variables will be presented along with their 2-sided 95% CI using the Brookmeyer and Crowley method.

Descriptive statistics will be provided for time to objective response and time to PSA response. Only responders will be included in analyses for DOR, duration of PSA response, time to response, and time to PSA response.

The ORR as assessed by investigator and its exact 2-sided 95% CI will be reported.

Pharmacokinetic Analyses:

Pamiparib concentrations will be summarized by nominal time of collection. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study in an existing model. Additional PK parameters such as apparent clearance (CL/F) of the drug from plasma and area under the plasma concentration-time curve from 0 to 12 hours postdose (AUC_{0-12}) may be derived from the population PK analysis if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results of the population PK and exposure-response analyses may be reported separately from the clinical study report.

Exploratory Efficacy Analyses:

[redacted]

[redacted]

Safety Analysis:

All TEAEs including, serious AEs, deaths, ≥ Grade 3 TEAEs, pamiparib-related TEAEs, and TEAEs that led to pamiparib withholding or permanent discontinuation, will be summarized. Pamiparib exposure, vital sign measurements, electrocardiogram findings, and clinical laboratory results will also be summarized.

Sample Size:

This study is designed to provide adequate power for primary endpoints of ORR and PSA response rate. A sample size of approximately 100 patients is planned (at approximately 45 centers with a projected average enrollment of 2 to 3 patients per center).

Assuming ORR of 35% for pamiparib in CTC-HRD-positive patients versus 15% for historical control in patients with measurable disease, the study power is 88% using a binomial exact test and 1-sided type-I error of 0.025 with n = 50. The binomial exact 95% CI of 35% ORR is 22.1% to 49.8% with a sample size of 50 patients.

Assuming PSA response rate of 50% for pamiparib versus 30% for historical control in CTC-HRD-positive patients with or without measurable disease, a sample size of 80 patients in this population will provide 95% study power using a binomial exact test and 1-sided type-I error of 0.025. The binomial exact 95% CI of 50% response rate is 38.6% to 61.4% with n = 80.

To explore the efficacy of pamiparib in patients with CTC-HRD-negative, but BRCA1/2-mutant mCRPC with or without measurable disease, approximately 20 patients will be enrolled in these cohorts.

Interim Analysis:

A non-binding interim futility analysis will be performed among the first 20 patients enrolled in Cohorts 1 and 2 (Synopsis Table 1). If the confirmed PSA response rate is < 30% (< 6 responses), enrollment will be halted, and safety and efficacy data will be further evaluated before making the decision of stopping enrollment permanently. The decision to continue the enrollment may be made at any time the 6 confirmed PSA responses in Cohorts 1 and 2 can be documented; enrollment of all 20 patients is not required before determining further patient accrual.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AML	acute myeloid leukemia
AUC	area under the plasma concentration-time curve (drug exposure)
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours postdose
BPI-SF	Brief Pain Inventory Short Form
CI	confidence interval
CKD-EPI	Chronic Kidney Epidemiology Collaboration
CR	complete response
CT	computed tomography
CTC	circulating tumor cell
CTC-HRD-negative or CTC-HRD-	circulating tumor cells negative for homologous recombination deficiency per Epic Sciences assay
CTC-HRD-positive or CTC-HRD+	circulating tumor cells positive for homologous recombination deficiency per Epic Sciences assay
CYP	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End-of-Treatment (Visit)
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels Health Questionnaire
FDG	fluorine-18 [F-18]fluorodeoxyglucose
HBV	hepatitis B virus
HCV	hepatitis C virus
HRD	homologous recombination deficiency
IC_{50}	half-maximal inhibition concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Review Committee
mCRPC	metastatic castration-resistant prostate cancer
MDRD STUDY EQ	Modification of Diet in Renal Disease study equation
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
pamiparib	BGB-290
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PET	positron-emission tomography
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SD	stable disease
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US or USA	United States or United States of America

1. INTRODUCTION

1.1. Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide, with an estimated 1.6 million cases and 366,000 deaths worldwide and the leading cause of cancer death in men in 29 countries (Global Burden of Disease Cancer Collaboration 2017). Rates of prostate cancer differ by over 25-fold in various countries around the world, with the highest incidence in Australia and western regions of the world such as the United States of America (USA) and Europe, and the lowest in Asian countries such as Japan, India, Hong Kong, and China (GLOBOCAN 2012; Crocetti 2015; SEER 2017; Gronberg 2003). Interpretation of these vast differences between regions may be accounted for by the increase in screening by prostate-specific antigen (PSA) and subsequently increased biopsies in Western countries compared with Asia. In the USA, prostate cancer is most commonly diagnosed in Black and non-Hispanic men who are 65 to 74 years of age, with a median diagnosis at 66 years age of and a median age of 80 years at death (SEER 2017).

Patients who have evidence of progressive disease (PD) (eg, increase in serum PSA, new metastases, and/or progression of existing metastases) while being managed with androgen deprivation therapy are considered to have castration-resistant prostate cancer.

For the past decade, the first-line treatment for metastatic castration-resistant prostate cancer (mCRPC) has been taxane-based treatments such as docetaxel and cabazitaxel in combination with prednisone. However, most patients develop resistance to these treatments and die within 2 to 3 years after initiation of treatment. Until recently, therapeutic options for docetaxel resistance were very limited in patients with mCRPC, but improvements in the understanding of castration-resistant prostate cancer biology led to the development of novel therapeutic agents that target the androgen receptor signaling pathway, such as abiraterone acetate and enzalutamide. Because men with mCRPC persistently maintain androgen receptor activity, despite castration levels of serum testosterone, novel androgen receptor-targeted agents can be effective for men with disease that is already resistant to androgen deprivation therapy.

Several key Phase 3 randomized, controlled studies have revealed that these novel drugs significantly improved the survival of mCRPC patients in either pre- or post-chemotherapeutic settings. However, various androgen receptor-targeting drugs, including abiraterone acetate, enzalutamide, and orteronel (TAK-700), have shown inconsistent therapeutic effects on oncological outcomes in patients with mCRPC. Thus, no consensus has been reached regarding the agent that provides the best oncological outcomes (Kang et al 2017).

1.2. Poly (ADP-ribose) Polymerase Inhibitors

Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA replication, transcriptional regulation, and DNA damage repair. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP-ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA. Inhibition of PARP converts common single-strand DNA breaks into double-strand breaks during

DNA replication. Small molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effects by interfering with DNA repair mechanisms. Since the discovery of synthetic lethality of PARP inhibitors in BRCA-deficient cells and, more broadly, cells with homologous recombination deficiency (HRD), accumulation of unrepaired single-strand DNA breaks resulting from catalytic PARP inhibition has been considered central to the mechanism of action of PARP inhibitors. More recently, it has been demonstrated that PARP inhibitors also trap PARP1- and PARP2-DNA complexes at DNA damage sites and that PARP trapping can be more cytotoxic than unrepaired single-strand DNA breaks (Pommier et al 2016; O'Connor 2015; Lord and Ashworth 2017).

In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses when used as a single agent in patients with BRCA1- or BRCA2-mutated tumors, while also achieving a favorable safety profile. Olaparib has been approved in the USA as a single agent for advanced ovarian cancer patients with a deleterious germline BRCA mutation; whereas, rucaparib has been approved for patients with a deleterious germline or somatic BRCA mutation (Lynparza [olaparib] prescribing information 2017; Rubraca [rucaparib] prescribing information 2018). Niraparib was approved by the US Food and Drug Administration in 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response (CR) or partial response (PR) to platinum-based chemotherapy (Zejula [niraparib] prescribing information 2017).

1.3. Biology of BRCA+ Prostate Cancers and PARP Inhibitors

Men with a BRCA2 mutation have a 5- to 9- fold increased risk of developing prostate cancer by age 65, perhaps translating to a risk of about 33% (Kote-Jarai et al 2011; Breast Cancer Linkage Consortium 1999). The risk of prostate cancer in men with a BRCA1 mutation is less clear, but also appears to be elevated by about 3.75-fold, translating to a risk of about 9% by age 65 (Leongamornlert et al 2012). In addition, men with metastatic prostate cancer and a BRCA2 mutation are known to have a poorer prognosis and overall survival (OS) compared with those without a BRCA2 mutation (Castro et al 2013). Furthermore, preliminary results have shown that these men may respond to treatment with a PARP inhibitor (Sandhu et al 2013a).

Other DNA-repair gene mutations may also occur more frequently in men with aggressive prostate cancer, but there are no data on the activity of PARP inhibitors in patients with mutations in other DNA repair genes (Pritchard et al 2016).

The PARP inhibitor olaparib was studied in 49 evaluable men with castration-resistant prostate cancer (Mateo et al 2015). In this Phase 2 study, all patients had received at least 2 prior regimens for castration-resistant disease and all had received prior docetaxel chemotherapy. All patients had tissue assessed for the presence of abnormalities in a predetermined panel of DNA-repair genes. Abnormalities were detected in 16 patients (33%), the most common of which were in BRCA2.

The primary endpoint of the study was a composite response rate that included objective response (Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) in those with assessable disease, a ≥ 50% decrease in serum PSA or a confirmed reduction in circulating tumor cells (CTCs)

from ≥ 5 cells per 7.5 mL of blood to < 5 cells per 7.5 mL. Among the men with a DNA repair gene abnormality, 14 (88%) had a response based upon these criteria. By contrast, only 1 of 33 (3%) without an identified DNA-repair gene abnormality responded. Radiographic progression-free survival (rPFS) was significantly longer in those with biomarker-positive disease compared with biomarker-negative disease (9.8 versus 2.7 months), as was OS (13.8 versus 7.5 months).

In a Phase 2 study, 153 men with castration-resistant prostate cancer were randomly assigned to abiraterone plus prednisone or to abiraterone, prednisone, and veliparib (Hussain et al 2018). There were no significant differences in the PSA response rate with or without the addition of veliparib (72% versus 64%, respectively) or in progression-free survival (11 versus 10.1 months). A defect in a DNA repair gene was present in 20 of 75 evaluable patients (27%), and in these patients, the differences in the PSA response rates with or without the addition of veliparib (90% versus 56%, respectively) and measurable disease response rates (88% versus 38%) were statistically significant.

In a Phase 2 study of men with mCRPC, 142 patients were randomly assigned to receive olaparib and abiraterone (n = 71) or placebo and abiraterone (n = 71). Median rPFS was 13.8 months (95% confidence interval [CI]: 10.8% to 20.4%) with olaparib and abiraterone and 8.2 months (95% CI: 5.5% to 9.7%) with placebo and abiraterone (hazard ratio 0.65, 95% CI: 0.44% to 0.97%, p = 0.034) (Clarke et al 2018).

Niraparib is a third PARP inhibitor. In a Phase 1 dose-escalation study, niraparib showed evidence of activity in prostate cancer patients with mutations in BRCA1 or BRCA2 (Sandhu et al 2013b). Currently a Phase 2 study with niraparib in mCRPC patients with DNA-repair anomalies is ongoing.

1.4. Circulating Tumor Cells as a Biomarker in Metastatic Castration-Resistant Prostate Cancer

Precision-based therapeutics targeting specific genomic alterations offer great promise for men with mCRPC. However, current approaches for genomic characterization are primarily tissue-based and are hindered by the low overall success rate (64%) for CT-guided bone biopsies in men with mCRPC for isolation of molecular material for sequencing as well as the high failure rate (58%) of sequencing bone-derived DNA (Holmes et al 2017; Cheng et al 2017). Efforts to utilize circulating tumor DNA for HRD determination in men with mCRPC, while having the potential to overcome the obstacles of obtaining bone-derived DNA for sequencing-based HRD determination, are hindered by limitations in detecting critical chromosomal rearrangements and copy-number variations (eg, BRCA deletions) (Hoppe et al 2018). Finally, DNA sequencing-based approaches for HRD determination using fixed gene panels, irrespective of sample analyte, are limited by the known biology of HRD and may not accurately predict clinical response in mCRPC (Hoppe et al 2018). As such, HRD determination using the phenotypic characterization of HRD+ CTCs may have significant clinical utility in the setting of mCRPC.

A recent meta-analysis conducted across 5 randomized Phase 3 clinical studies suggests that CTC enumeration may be a robust predictor of OS in mCRPC (Heller et al 2018). Furthermore, CTC-based detection of the AR-V7 mRNA assay has been shown to be prognostic in men with mCRPC treated with first- and second-line abiraterone and enzalutamide (Antonarakis et al 2017). HRD status in

patients was assessed using a quantitative CTC biomarker assay that detects HRD+ CTCs in whole blood based on their phenotypic features. This assay, recently shown to predict response to veliparib in men with mCRPC (Dittamore et al 2018), utilizes an analytically validated microscopy-based CTC detection technology (Werner et al 2015; Scher et al 2017) for the identification of CTCs from whole blood, and subsequent computer vision/digital pathology based characterization of each identified CTC to asses HRD specific features.

Historically, distinct patterns of genomic alterations have been used to identify HRD in tumors (Marquard et al 2015). CTCs positive for these genomic alterations have also been associated with HRD were previously shown (Feng et al 2016; Scher et al 2017) to have specific phenotypic features when measured by US Food and Drug Administration cleared digital pathology methods (Wilbur et al 1998; O'Leary et al 1998; Biscotti et al 2005). Applied here, the CTC-HRD-positive (circulating tumor cells positive for homologous recombination deficiency per Epic Sciences assay) classifier will be used to identify patients for PARP inhibition based on the prevalence of CTCs with these phenotypic features.

1.5. PARP Inhibitor Pamiparib

1.5.1. Nonclinical Data for Pamiparib

Pamiparib is a potent and selective inhibitor of PARP1 and PARP2 that combines potent PARP-trapping activity with significant brain penetrance.

1.5.1.1. Nonclinical Safety Data

[redacted]

[redacted]

In summary, all available toxicologic studies and data are adequate to support clinical development of pamiparib for treatment of patients with advanced cancer. Please refer to the Pamiparib Investigator's Brochure for additional information.

1.5.1.2. Nonclinical Activity Data

[redacted]

[redacted]

[redacted]

Please refer to the Pamiparib Investigator's Brochure for additional information.

1.5.2. Clinical Data for Pamiparib

There are 5 ongoing studies with pamiparib with available preliminary data: ongoing monotherapy studies BGB-290-AU-002 and BGB-290-102; and combination therapy studies BGB-290-103 (pamiparib in combination with temozolomide), BGB-290-104 (pamiparib in combination with radiation and/or temozolomide), and BGB-A317/BGB-290_Study_001 (pamiparib in combination with the anti-PD-1 antibody tislelizumab [also known as BGB-A317]). The study data from BGB-290-AU-002 are the most mature and interim results are summarized below.

1.5.2.1. Pharmacokinetics Data for BGB-290-AU-002

1.5.2.2. Exploratory Biomarker Data

[redacted]

1.5.2.3. Clinical Safety and Preliminary Efficacy for BGB-290-AU-002

BGB-290-AU-002 is a Phase 1a/1b study to evaluate the safety, PK, food effect, and antitumor activity of pamiparib in patients with advanced solid tumors. The Phase 1A portion is a first-in-human study evaluating pamiparib to characterize the safety, the maximum tolerated dose, preliminary antitumor activity, and the PK of pamiparib given as a monotherapy in a 3+3 dose escalation scheme. In Phase 1a Part 1, pamiparib was administered in doses ranging from 2.5 to 120 mg orally twice a day.

The study is being conducted in Australia. Preliminary data for 45 patients in the Phase 1a Part 1 portion of the study are available (cutoff date of 01 December 2017) and are presented below unless noted otherwise.

The preliminary safety data indicate that the most frequent nonhematologic adverse events (AEs) (≥ 10% of patients) were nausea (64%, n = 29), vomiting (36%, n = 16), fatigue (33%, n = 15), diarrhea (29%, n = 13), abdominal pain (22%, n = 10), constipation, urinary tract infection (each 18%, n = 8), upper respiratory tract infection (16%, n = 7), ascites, pyrexia, headache, and decreased appetite (each 11%, n = 5).

Hematologic AEs are of interest in this study. Anemia was most frequent (33%, n = 15), followed by neutropenia (11%, n = 5) and platelet count decreased (4%, n = 2).

Twenty-seven (60%) patients experienced ≥ Grade 3 AEs (regardless of relatedness). Ten (22%) patients experienced ≥ Grade 3 AEs that were considered related to pamiparib by the investigator: anemia (13%, n = 6), neutropenia (7%, n = 3), nausea, fatigue, diarrhea, oral paresthesia, paresthesia, and hypophosphatemia (each 2%, n = 1).

Serious AEs (SAEs) were reported in 25 (56%) patients, and for 3 (7%) patients they were considered related to pamiparib by the investigator: anemia (4%; n = 2) and nausea (2%; n = 1). Three (7%) patients discontinued study drug because of an AE: vomiting, paresthesia of the hands and mouth, and traumatic hematoma (due to a fall) (each n = 1).

Overall, 4 patients in the entire study experienced a fatal AE: 1 AE of pleural effusion in a breast cancer patient who died of PD complicated by respiratory failure; 1 AE of intestinal obstruction in an ovarian cancer patient; 1 AE of intestinal perforation in an ovarian cancer patient; and 1 AE of gastric obstruction in a fallopian tube cancer patient. All 4 fatal events were assessed by the investigator as not related to pamiparib.

Four patients experienced AEs that were considered dose-limiting toxicities: Grade 2 nausea in 2 patients; Grade 2 anorexia and Grade 2 nausea in 1 patient; and Grade 2 nausea, Grade 3 fatigue, and Grade 3 paresthesia in 1 patient. Based on the encountered dose-limiting toxicities and the overall safety profile of pamiparib, the maximum tolerated dose of pamiparib was determined to be 80 mg orally twice a day (160 mg/day).

Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) are recognized AEs in patients receiving PARP inhibitors (Ricks et al 2015). To date, no cases of MDS or AML have been observed in any study that includes pamiparib.

In the Phase 1A portion of the study, 10 patients achieved either a CR (n = 3) or PR (n = 7); all responses were observed in patients with gynecologic cancers.

1.6. Rationale for Selection of Pamiparib Dose

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose of pamiparib 60 mg orally twice a day was selected using available clinical data from Study BGB-290-AU-002 (Section 1.5.2.3). The study determined the maximum tolerated dose of pamiparib to be 80 mg orally twice a day (160 mg/day). The dose of 60 mg twice a day was selected for further evaluation based on the following findings (refer to the Pamiparib Investigator's Brochure):

- A linear PK profile observed up to 80 mg twice a day
- Overlapping pamiparib exposure among patients treated with 40 mg, 60 mg, and 80 mg twice a day
- Similar toxicity profiles at 60 mg and 80 mg twice a day with the following differences:
    - Fewer patients at 60 mg twice a day experienced treatment-related treatment-emergent adverse events (TEAEs) of anemia and neutropenia.
    - There was a slightly higher rate of dose interruptions at 80 mg versus 60 mg twice a day for anemia and nausea.
- Responses were observed across the dose range evaluated

1.7. Study Rationale

For men with advanced prostate cancer, androgen deprivation therapy usually can provide disease control for a substantial period of time. However, most men eventually develop PD that is resistant to further hormonal treatment. A number of new therapies (including anti-androgen treatments) have been shown to prolong survival in this setting, but there remains a need for additional approaches that can control disease and prolong survival.

An increasing understanding of the biology of prostate cancer is leading to the development of new therapies that can target specific abnormalities in prostate cancer, such as HRD. As stated earlier, men with metastatic prostate cancer and a BRCA2 mutation are known to have a poorer prognosis and OS compared with those without a BRCA2 mutation. As discussed in Section 1.3, preliminary results have shown that these patients may respond to treatment with a PARP inhibitor as these specifically target cancers with HRD. However, remaining challenges are obtaining adequate tumor material for successful sequencing, in addition to identifying the correct patients whose tumors are bona fide HRD.

The aim of this study is to assess the efficacy of pamiparib in mCRPC patients with disease progression as assessed by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria and with homologous recombination deficiency (HRD-positive) by Epic Sciences assay; thus, establishing the association between CTC-HRD status and pamiparib activity.

1.8. Risk-Benefit Assessment

Pamiparib has been studied in nonclinical toxicity and Phase 1 clinical studies. Pamiparib toxicities are largely consistent with the safety profile shared by other PARP inhibitors. The safety profile and adverse drug reactions observed in patients treated with pamiparib monotherapy are summarized in Section 6, Summary of Data and Guidance for the Investigator of the Pamiparib Investigator's Brochure.

MDS and AML have been reported in a small number (< 1%) of patients treated with PARP inhibitors, especially in patients harboring a germline BRCA mutation (Ricks et al 2015). Typically, patients who develop MDS and AML while on therapy with a PARP inhibitor have a history of extensive previous chemotherapy and some have a history of previous cancer or bone marrow abnormalities. To date, there have been no reports of MDS or AML in patients treated with pamiparib and no fatal adverse drug reactions. Patients in this study will be monitored monthly for hematologic toxicities and events of MDS and AML will be reported as SAEs.

Preliminary data from ongoing monotherapy studies show that pamiparib appears to be generally well tolerated in patients with advanced solid tumors. The safety profile for single-agent pamiparib is similar to those observed in other PARP inhibitors. Some antitumor activity has been observed across the dose ranges evaluated in patients. Therefore, the risk-benefit profile for pamiparib monotherapy is considered acceptable in a patient population with metastatic cancer.

1.9. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and regulatory authorities, and in accordance with Good Clinical Practice standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the efficacy of pamiparib in patients with metastatic castration-resistant prostate cancer (mCRPC) positive for circulating tumor cells with homologous recombination deficiency (CTC-HRD-positive; per Epic Sciences assay), as per Prostate Cancer Clinical Trials Working Group [PCWG3] criteria

2.1.2. Secondary Objectives

- To further evaluate the efficacy of pamiparib in patients with CTC-HRD-positive mCRPC with measurable disease (Cohort 1 of Table 2), as per PCWG3 criteria
- To further evaluate the efficacy of pamiparib in patients with CTC-HRD-positive mCRPC with or without measurable disease (Cohorts 1 and 2 of Table 2, respectively), as per PCWG3 criteria
- To evaluate the safety and tolerability of pamiparib

2.1.3. Exploratory Objectives

- [redacted]

2.2. Study Endpoints

Assessments are per the investigator except when indicated otherwise. Assessments will be conducted in accordance with Good Clinical Practice and all applicable regulatory requirements.

2.2.1. Primary Endpoints

- Objective response rate (ORR; defined as the proportion of patients with best objective response of CR or PR confirmed at a subsequent timepoint ≥ 4 weeks later) by Independent Review Committee (IRC) for CTC-HRD-positive patients with measurable disease (Cohort 1 of Table 2)
- Prostate-specific antigen (PSA) response rate (defined as the proportion of patients with PSA decline ≥ 50% from baseline [confirmed by a second PSA value ≥ 3 weeks later]) for CTC-HRD-positive patients with or without measurable disease (Cohorts 1 and 2 of Table 2, respectively)

2.2.2. Secondary Endpoints

Patients with CTC-HRD-Positive mCRPC with Measurable Disease (Cohort 1 of Table 2) per PCWG3 Criteria

- Duration of response (DOR) by IRC
- ORR by investigator
- Time to objective response
- Clinical benefit rate (defined as the proportion of patients with a documented confirmed CR, PR, or stable disease)

Patients with CTC-HRD-Positive mCRPC with or without Measurable Disease (Cohorts 1 and 2 of Table 2, respectively) per PCWG3 Criteria

- Time to PSA response
- Duration of PSA response
- Time to PSA progression (defined as the time from the date of the first dose of study drug to a ≥ 25% increase in PSA with an absolute increase of ≥ 2 ng/mL above the nadir [or above the baseline for patients with no PSA decline after 12 weeks], confirmed by a second value ≥ 3 weeks later)
- Time to symptomatic skeletal event (SSE; defined as the time from the date of the first dose of study drug to the first symptomatic fracture, radiation or surgery to bone, or spinal cord compression)
- Radiographic progression-free survival (rPFS; defined as the time from the date of the first dose of study drug to radiographic disease progression by IRC or death due to any cause, whichever occurs first)
- Overall survival (OS)

All Patients (Cohorts 1, 2, 3, and 4 of Table 2)

- Incidence, timing, and severity of TEAEs, graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 or higher

2.2.3. Exploratory Endpoints

- [redacted]

[redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, single-arm, global Phase 2 study to evaluate the efficacy and safety of single-agent poly (ADP-ribose) polymerase 1 and 2 (PARP1/2) inhibitor pamiparib in mCRPC patients with CTC-HRD-positive disease or who have a deleterious germline or somatic mutation in BRCA1 or BRCA2.

To be eligible for the study, biomarker-positive patients must have progressed on or after at least one androgen receptor-targeted therapy for mCRPC (eg, enzalutamide, abiraterone acetate/prednisone, bicalutamide, flutamide, apalutamide, or nilutamide), received at least 1 taxane-based therapy for metastatic prostate cancer, and have PSA progression as per PCWG3 criteria at time of study entry. The primary endpoints are ORR by IRC for patients with measurable disease ($n \approx 50$) and PSA response rate for patients with or without measurable disease ($n \approx 80$) as per PCWG3 criteria.

Cohort 1 will include 50 mCRPC patients with CTC-HRD-positive, measurable metastatic disease (soft tissue with/without bone lesions), and positive BRCA1/2 mutation or negative/unknown BRCA1/2 mutation. Cohort 2 will include 30 mCRPC CTC-HRD positive patients with bone metastasis only and positive or negative/unknown BRCA1/2. Cohort 3 and 4 will include 20 mCRPC CTC-HRD negative/unknown patients with BRCA1/2 positive mutations, metastatic disease (measurable soft tissue with/without bone), and bone only (see Table 2).

After enrollment, patients will receive pamiparib 60 mg orally twice a day in cycles of 28 days.

Safety assessments will occur on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and as needed. Dose modifications will be made if appropriate (Section 6.1.4). AEs will be followed and documented during the treatment phase and for approximately 30 days after the last dose of pamiparib or until initiation of new anticancer therapy, whichever occurs first (Section 9 and Appendix 1). AEs will be graded according to NCI-CTCAE Version 4.03 or higher. A Safety Monitoring Committee will periodically review safety data.

PK samples for pamiparib will be collected at various timepoints at all non-China centers and at centers with such capability in China. In addition, tumor tissue (if available) and blood samples will

be obtained to explore biomarkers of pharmacodynamics, response, and resistance to pamiparib in mCRPC.

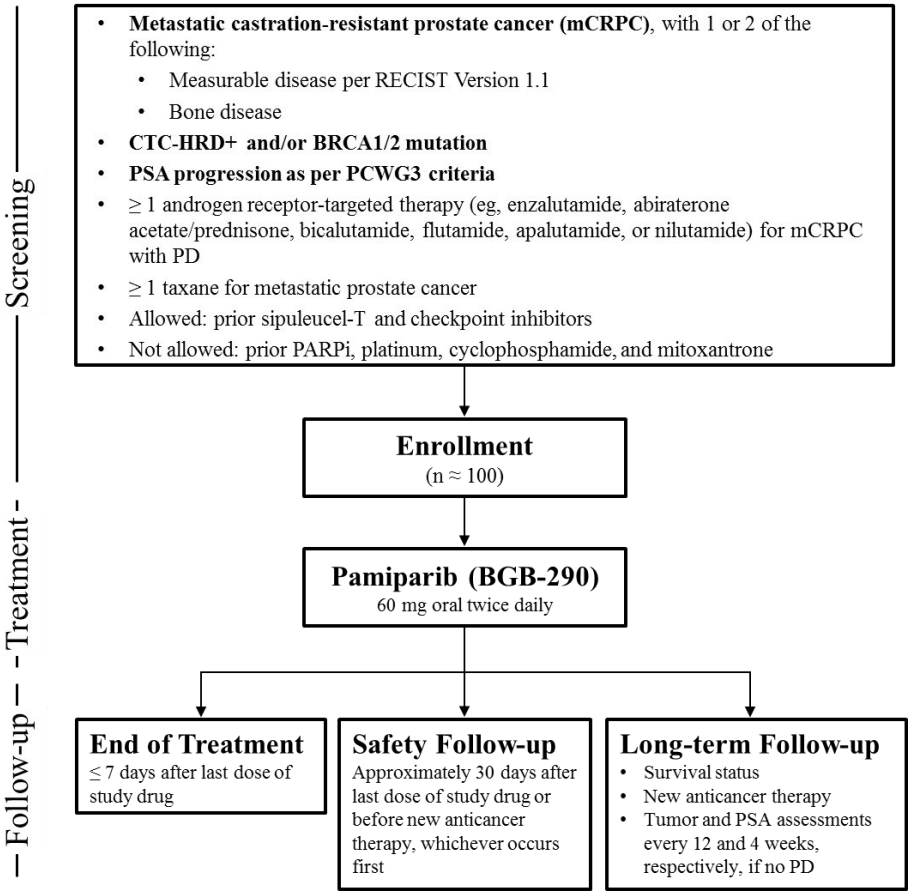
Disease status will be assessed by the investigator using PCWG3 criteria (Appendix 10). Patients will undergo tumor assessments every 8 weeks (± 7 days) for 24 weeks, then every 12 weeks (± 7 days), or as clinically indicated. PSA assessments will occur at screening, on Day 1, and then every 4 weeks (± 7 days), or as clinically indicated.

Administration of pamiparib will continue until PD, unacceptable toxicity, death, or another discontinuation criterion is met (Sections 5.5.1 and 5.6.4). Once the treatment phase has been completed, an End-of-Treatment (EOT) Visit should occur within 7 days of stopping pamiparib with subsequent phases of safety and long-term follow-up.

Long-term follow-up will include tumor and PSA assessments every 12 weeks and 4 weeks (± 7 days), respectively, for those patients without PD, survival status, and initiation of new anticancer therapy. Long-term follow-up will continue until the patient dies or another criterion for discontinuation from study is met (Section 5.6.4).

Study procedures and assessments are detailed in Section 7 and Appendix 1. The patient cohorts are presented in Table 2 and study schema is presented in Figure 2.

Figure 2: Study Schema



Abbreviations: CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay; mCRPC, metastatic castration-resistant prostate cancer; PARPi, PARP inhibitor; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, progressive disease; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.
Notes: Key assessments during the treatment phase: tumor assessments every 8 weeks (± 7 days) for 24 weeks, then every 12 weeks (± 7 days), or as clinically indicated; and patient-reported outcomes, PSA, adverse events, hematology, and chemistry every 4 weeks. Pamiparib is to be administered continuously.

Table 2: Patient Cohorts

Cohort	1		2		3	4
Patients	n ≈ 50		n ≈ 30		n ≈ 20	
CTC-HRD	+		+		-/∅	
Metastatic disease	Measurable soft tissue ± bone		Bone only		Measurable soft tissue ± bone	Bone only
BRCA1/2 mutation	1A: +	1B: -/∅	2A: +	2B: -/∅	+	

Abbreviations: ∅, biomarker status unknown; CTC-HRD-, negative for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay; CTC-HRD+, positive for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay.

3.2. Safety Monitoring Committee

The Safety Monitoring Committee will be composed, at a minimum, of clinicians and a statistician. These members will have experience in the fields of oncology, clinical study conduct and monitoring, and biostatistics.

The Safety Monitoring Committee will provide safety oversight for the study population and will advise the study team of the need for study modification or termination based on regular reviews of accumulating safety data. Regular safety monitoring will be performed by the Safety Monitoring Committee. Details of the membership, scope of data review, and meeting frequency will be provided in the Safety Monitoring Committee charter.

Following Safety Monitoring Committee review and discussion, the sponsor will make final decisions regarding any change in the study conduct. Please see the details in the Safety Monitoring Committee charter.

3.3. Independent Review Committee

Tumor images will be collected and reviewed by the IRC for baseline tumor status during screening, on-study tumor monitoring, and adjudication of the selected efficacy endpoints. The protocol-specific review function and processes of the IRC will be described in the IRC charter.

3.4. Duration of the Study

The duration of the study from first enrolled patient to last patient is off study is estimated to be approximately 31 months.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Sign informed consent form (ICF): must be able to provide written informed consent and can understand the nature, significance, and consequences of participating in the clinical study
2. Agrees not to participate in another interventional study while on pamiparib
3. If receiving bisphosphonate or other approved bone-targeting therapy, must have been on stable doses for at ≥ 28 days before start of pamiparib on Day 1
4. Adult males ≥ 18 years of age at the time of informed consent and has signed informed consent before any study-related activities and according to local guidelines
5. Histologically or cytologically confirmed adenocarcinoma or poorly differentiated adenocarcinoma of the prostate without neuroendocrine differentiation
    - Mixed histology is acceptable.
    - Pure small cell histology is excluded.

6. Metastatic castration-resistant prostate cancer (mCRPC) with 1 or 2 of the following:
    a) Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Appendix 2), involving viscera (lung, liver, adrenal glands, or other) and/or extrapelvic nodes (retroperitoneal, mediastinal, thoracic, or other)
    b) Bone disease
7. Prostate cancer progression defined as follows:
    a) Prostate-specific antigen (PSA) progression with ≥ 3 rising PSA levels with ≥ 1 week between determinations
    b) Screening PSA ≥ 2 µg/L (2 ng/mL)
8. Surgical or medical castration (bilateral orchiectomy or ongoing treatment with a gonadotropin-releasing hormone [GnRH] agonist or antagonist, respectively)
9. Serum testosterone ≤ 1.73 nmol/L (or ≤ 50 ng/dL) at screening
10. ≥ 1 androgen receptor-targeted therapy for mCRPC (eg, enzalutamide, abiraterone acetate/prednisone, bicalutamide, flutamide, apalutamide, or nilutamide)
11. ≥ 1 taxane-based therapy for metastatic castration-resistant prostate cancer
12. Prostate cancer with homologous recombination deficiency (HRD) as evidenced by 1 or 2 of the following:
    a) Positive for circulating tumor cells with homologous recombination deficiency per Epic Sciences assay (CTC-HRD-positive)
    b) Deleterious germline or somatic mutation in BRCA1 or BRCA2
13. Agreement to provide tumor tissue, if available, and blood samples for molecular analysis
    - Note: If archival tumor tissue is not available, an optional fresh biopsy is highly recommended.
14. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Appendix 3)
15. Ability to swallow whole capsules
16. Ability to comply with study requirements and complete study questionnaires
17. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 14 days before Day 1):
    a) Absolute neutrophil count ≥ 1.5 x 10^9/L
    b) Platelet count ≥ 100 x 10^9/L
    c) Hemoglobin ≥ 9 g/dL (≥ 28 days after growth factor support or transfusion)
    d) Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 11)
    e) Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)

- ≤ 4 x ULN, if Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of elevation

f) Aspartate and alanine aminotransferase ≤ 3 x ULN

- ≤ 5 x ULN for a patient with liver metastases

18. Nonsterile males and female partners of nonsterile male study patients must agree to practice highly effective methods of birth control (Appendix 4) for the duration of the study and for at least 6 months after the last dose of pamiparib. Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after the last dose of pamiparib.

4.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. Unresolved acute adverse effects of prior therapy of ≥ Grade 2
   - Except for AEs not considered a likely safety risk by investigator judgement (eg, alopecia, neuropathy, and specific laboratory abnormalities)
2. Chemotherapy, hormonal therapy, biologic therapy, radionuclide therapy, immunotherapy, investigational agent, Chinese anticancer medicine, or herbal remedies ≤ 5 half-lives if the half-life is known, ≤ 14 days if not known, before Day 1
   - Continued treatment with a bisphosphonate or denosumab is allowed, if administered at a stable dose ≥ 28 days before Day 1
3. Radiotherapy ≤ 21 days (≤ 14 days, if a single fraction of radiotherapy) before Day 1
4. Prior treatment for prostate cancer with any of the following:
   a) PARP inhibitor
   b) Platinum
   c) Cyclophosphamide
   d) Mitoxantrone
   - Prior treatment with sipuleucel-T or a checkpoint inhibitor (eg, nivolumab or pembrolizumab) is allowed.
5. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 14 days before Day 1, or anticipation of need for major surgical procedure during the course of the study
   - Placement of a vascular access device is not considered major surgery.
6. Diagnosis of myelodysplastic syndrome (MDS)
7. Other diagnosis of malignancy (including, but not limited to AML)
   - Except for surgically excised nonmelanoma skin cancer, adequately treated non-invasive bladder cancer, or a malignancy diagnosed > 2 years ago with no current evidence of disease and no therapy ≤ 2 years before Day 1
8. Leptomeningeal disease or uncontrolled, untreated brain metastases

- Patients with a history of treated and, at the time of screening, asymptomatic brain metastases are eligible, provided they meet all of the following:
  - Only supratentorial metastases
  - Brain imaging at screening without evidence of interim progression
  - No ongoing requirement for corticosteroids as therapy for brain metastases
    - Anticonvulsants at a stable dose allowed
  - No stereotactic radiation or whole-brain radiation ≤ 14 days before Day 1

9. Active infection requiring systemic treatment, acute/viral hepatitis or active chronic hepatitis B or C infection, or active tuberculosis
   - Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL or patients with active hepatitis C should be excluded. Note: Inactive hepatitis B surface antigen carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL), and cured hepatitis C patients can be enrolled.
10. Any of the following cardiovascular criteria:
    a) Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before Day 1
    b) Symptomatic pulmonary embolism ≤ 28 days before Day 1
    c) Any history of acute myocardial infarction ≤ 6 months before Day 1
    d) Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 5) ≤ 6 months before Day 1
    e) Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before Day 1
    f) Any history of cerebral vascular accident ≤ 6 months before Day 1
11. Previous complete gastric resection, chronic diarrhea, active inflammatory gastrointestinal disease, or any other disease-causing malabsorption syndrome
    - Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed.
12. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months before Day 1
13. Use ≤ 5 half-lives if the half-life is known, ≤ 14 days if not known, before Day 1 or anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP) 3A inhibitors or strong CYP3A inducers (Appendix 6)
14. Serum creatinine > 2.5 mg/dL at screening
15. Significant intercurrent illness that may result in the patient's death before death from prostate cancer
16. Known history of intolerance to the excipients of the pamiparib capsule

5. STUDY PHASES FROM SCREENING TO END OF STUDY

5.1. Screening

As part of the Screening Visit, study center personnel will explain to the potential patient all aspects of the study, obtain signed informed consent, and document the informed consent process in the patient's source documents before any study-specific procedures are conducted. The signed ICF initiates screening that must occur within 28 days before Day 1.

Required screening assessments, some with shorter screening windows, are listed in Appendix 1. Assessments obtained within 7 days of Day 1 do not have to be repeated on Day 1. Patient treatment authorization may occur as late as Day 1 before the first dose of pamiparib. Results of standard of-care tests or examinations performed before obtaining informed consent and within the screening windows may be used and do not have to be repeated as long as they meet protocol specifications.

The investigator and study center radiologist will assess the potential patient for eligibility. Repeating screening assessments within the original screening window is allowed if the patient did not previously meet certain eligibility criteria. Tumor assessments should not be repeated. Screen failures and consent withdrawals will be documented in the patients' source documents.

5.2. Enrollment

After consent has been obtained, each patient will be assigned a unique patient number that cannot be reassigned to any other patient. Patient numbers will be assigned in chronological order starting with the lowest number. After determination of eligibility, the investigator will complete the supporting documentation and provide them to the sponsor and/or designee for review and subsequent approval. No eligibility waivers will be granted.

5.3. Treatment Phase

The treatment phase is defined as the time elapsed between the first dose of pamiparib and the last dose of pamiparib administered.

Day 1 of Cycle 1 is the first day of pamiparib administration (there is no Day 0 in this protocol). Patients must initiate study treatment within 4 days after authorization for treatment.

Study procedures of each clinic visit are outlined in Appendix 1.

Assessments should be obtained before pamiparib administration unless stated otherwise in Appendix 1 and should be performed in order of least invasive to most invasive assessment. All safety-related assessments must be reviewed and dose modifications, if necessary, be made by the investigator or subinvestigator before pamiparib administration.

Patient-reported outcome questionnaires should be completed before any other study activities occur.

Pamiparib dosing should be interrupted if at least 1 of the reasons listed in Section 5.5.1 is present, and the reason(s) for interruption should be recorded in the source document and in the corresponding electronic case report form (eCRF).

5.4. Unscheduled Visit

Unscheduled visits may occur at any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow up of AEs. Study assessments of an unscheduled visit should be performed based on the reason for the unscheduled visit and are outlined in Appendix 1. If PD is suspected, imaging studies should be performed and blood for biomarkers should be obtained as appropriate.

5.5. Permanent Discontinuation of Pamiparib

5.5.1. Reasons for Permanent Discontinuation of Pamiparib

Patients may permanently discontinue pamiparib for any of the following reasons:

- PD
- AEs
    - AEs that could lead to discontinuation of study drug are described in Table 4 within Section 6.1.4
- Major protocol deviation
- Patient withdrew consent for study treatment
    - Patients may voluntarily withdraw consent from study treatment at any time
    - Patients should be requested to participate in the follow-up phase, if patient withdraws consent from the treatment phase only
- Investigator's discretion
- Initiation of new anticancer therapy

The reason for permanent discontinuation of pamiparib will be recorded on the eCRF. Patients may discontinue pamiparib for other reasons but these will result in premature discontinuation from study (Section 5.6.4).

5.5.2. End-of-Treatment Visit

The EOT Visit should occur within 7 days after pamiparib has been permanently discontinued. Required assessments are listed in Appendix 1. A visit should be scheduled as soon as possible, but the EOT Visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which tumor assessments showed PD may be used as the EOT Visit if all required assessments were performed. Tumor assessments do not have to be repeated if they were performed within 14 days of the EOT Visit or at a prior response evaluation that documented PD. An ECG does not have to be repeated if it was performed within 14 days of the EOT Visit.

5.6. Follow-Up Phase

5.6.1. Safety Follow-up

All patients who permanently discontinue pamiparib and have not initiated new anticancer therapy will be followed for AEs and SAEs as outlined in Section 9.3.1. Approximately 30 days after the last dose of pamiparib or before initiation of new anticancer therapy, whichever occurs first, the Safety Follow-up Visit will occur with the safety assessments outlined in Appendix 1. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible.

For patients who do not want to or cannot return to the clinic for the Safety Follow-up Visit, the patient should be contacted by telephone for a review of AEs. If these attempts of contact are unsuccessful, the additional attempts detailed in Section 5.6.3 should be made.

5.6.2. Long-term Follow-up

Patients will be followed for survival and initiation of new anticancer therapy via telephone contact or other means (eg, clinic visit) approximately every 12 weeks (Appendix 1).

Patients who do not have objective disease progression at the time of pamiparib permanent discontinuation but meet other discontinuation criteria (eg, discontinued for AE and no new anticancer therapy) will continue to have tumor and PSA assessments every 12 weeks and 4 weeks (± 7 days), respectively, until PD or any other reason listed in Section 5.6.4, whichever occurs first. For efficacy assessments as per protocol, refer to Section 7.3 and Appendix 1. If the patient refuses to return for these PSA and tumor assessments or is unable to do so, every effort should be made to contact the patient by telephone to determine the patient's disease status and survival.

5.6.3. Lost to Follow-up

If a patient is lost to follow-up, study center personnel must do their utmost to re-establish contact with the patient and determine the reason for withdrawal. All measures taken to follow up with the patient should be recorded.

Should attempts to contact the patient by telephone be unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The patient should be contacted by mail in a manner that provides proof of receipt by the patient. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

5.6.4. Patient Discontinuation From Study (End of Study for an Individual Patient)

Premature discontinuation from the study (without EOT and any follow-up visits) will occur under the following circumstances:

- Patient withdrew consent for study participation

  - Patients may voluntarily withdraw consent from the study at any time
- Investigator's discretion
- Lost to follow-up
  - Lost to follow-up should be recorded as such in the eCRF
  - The investigator should show due diligence by documenting in the source documents steps taken to contact the patient (Section 5.6.3)
- Death
- Study termination by sponsor
- Other, as per the discretion of the sponsor or health authority

When a patient withdraws before the end of the study, the reason for withdrawal should be recorded in the source document and eCRF. Patients who withdraw from the study will not be replaced.

5.7. End of Study

The end of study is defined as the last patient last visit at the end of the long-term follow-up phase. This is the last timepoint for data collection. A patient is considered on study as long as the patient is still in long-term follow-up.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Evidence of no clinical benefit

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit and Safety Follow-up Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

The sponsor has the right to close a study center at any time. The decision will be notified to the center in advance. Reasons for closing a center may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Good Clinical Practice noncompliance
- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)]

6. STUDY TREATMENT

6.1. Study Drug

[redacted]

[redacted]

6.1.3. Dosage and Administration

Pamiparib capsules will be administered orally twice a day, once in the morning and once in the evening. The time difference between 2 consecutive doses should be approximately 8 to 12 hours.

Patients will be instructed to swallow the capsules whole, in rapid succession, with water. [redacted]

A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

6.1.4. Dose Hold and Modification

AEs should be assessed as best as possible regarding their relatedness to pamiparib. Patients should continue on study with follow-up as outlined in Sections 5.5 and 5.6.

Investigators should make every effort to maintain dose intensity in patients. Dosing of pamiparib can be withheld for up to 28 days consecutively. Dose reductions are allowed in 20 mg per dose decrements. If drug is held ≥ 28 days, the medical monitor must be contacted before permanent patient discontinuation from pamiparib.

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the investigator based on discussions with the medical monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicities related to pamiparib should be managed according to standard medical practice.

A maximum of 2 dose reductions is allowed before the patient must be permanently withdrawn from pamiparib. Dose levels for pamiparib are summarized in Table 3. Pamiparib will be dose modified as outlined in Table 4. For prolonged hematologic toxicities, interrupt treatment and monitor blood counts weekly until recovery. If the levels have not recovered to NCI-CTCAE Grade 1 or less after 4 weeks, further investigations should be considered, including bone marrow analysis and blood sample for cytogenetics. If MDS or AML is confirmed, discontinue pamiparib.

Table 3: Dose Levels for Pamiparib

Dose Level	Pamiparib
1	60 mg orally twice a day
-1	40 mg orally twice a day
-2	20 mg orally twice a day

Pamiparib may be dose-reduced for a maximum of 2 dose reductions.

Table 4: Criteria for Modification of Pamiparib Dosing for Related Adverse Events

Toxicity		Recommended Dose Modification[a]
Hematologic		
Anemia (hemoglobin)		
Hgb < 9.0 g/dL		• **First occurrence of Hgb < 9.0 g/dL:** Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, and then ↓ pamiparib by 1 dose level to 40 mg BID
Grade 2 (Hgb <10 - 8 g/dL)	Hgb <10 - 9 g/dL	Continue dosing at current dose level and treat with appropriate supportive care as medically indicated
	Hgb <9 - 8 g/dL	• **Subsequent occurrence following dose reduction for anemia:** o Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID
Grade 3 (Hgb <8 g/dL)		• **Subsequent occurrence following dose reduction for anemia:** o Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID
Grade 4 (life-threatening consequences; urgent intervention indicated)		• **Second occurrence following dose reduction for anemia:** o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID • **Third occurrence following 2 dose reductions for anemia:** o Discontinue pamiparib if anemia is not caused by any other confounding event, eg GI hemorrhage. o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level.
Note: 1) Weekly hematology test should be done for the first 3 cycles during the study. For all Grade 2 or higher anemia, hematology test should be done weekly thereafter until adequate recovery. 2) For any patients showing Hgb dropping > 2 g/dL especially within a short time without alternative explanation such as gastrointestinal bleeding, ↓ pamiparib by 1 dose level should be considered. 3) Dose increase can be considered in certain cases, depending on approval from the medical monitor, provided Hgb has been maintained above 9 g/dL for at least 3 months		

Toxicity	Recommended Dose Modification[a]
Neutropenia (absolute neutrophil count)	
Grade 3 (absolute neutrophil count < 1.0 - 0.5 x 10^9/L)	Hold pamiparib until resolved to ≤ Grade 2 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (absolute neutrophil count < 0.5 x 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Febrile neutropenia (absolute neutrophil count < 1.0 x 10^9/L with single temperature of > 38.3°C or sustained temperature of ≥ 38°C for > 1 hour)	Hold pamiparib until resolved and ↓ pamiparib by 1 dose level
Thrombocytopenia (platelet count)	
Grade 3 (platelet count < 50 - 25 x 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Grade 4 (platelet count < 25 x 10^9/L)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Renal	
Estimated glomerular filtration rate (CKD-EPI equation; Appendix 11)	
If ≥ 60 mL/min/1.73 m^2 at baseline: < 30 to 15 mL/min/1.73 m^2 or If < 60 mL/min/1.73 m^2 at baseline: ≥ 50% reduction from baseline	Hold pamiparib until resolved to ≥ 60 mL/min/1.73 m^2 • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Regardless of baseline: < 15 mL/min/1.73 m^2	Permanently discontinue pamiparib

Table 4: Criteria for Modification of Pamiparib Dosing for Related Adverse Events (Continued)

Toxicity	Recommended Dose Modification[a]
Hepatic	
Bilirubin	
Grade 2 (> 1.5 - 3.0 x ULN) *Only applies to patients with normal bilirubin at baseline*	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level

Toxicity	Recommended Dose Modification[a]
Grade 4 (> 10.0 x ULN)	Permanently discontinue pamiparib Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (eg, review of peripheral blood smear and haptoglobin determination), then ↓ pamiparib by 1 dose level and continue treatment at the discretion of the investigator in discussion with the medical monitor
Aspartate aminotransferase and/or alanine aminotransferase	
Grade 3 (> 5 and ≤ 20 x ULN)	Hold pamiparib until aspartate aminotransferase and/or alanine aminotransferase resolved to ≤ 5 x ULN or baseline • If not resolved within 7 days to ≤5 x ULN*, then pamiparib should be decreased by 1 dose level • If second episode, permanently discontinue pamiparib *if other etiologies have been reasonably excluded and not solely based on abnormality/increase of AST/ALT laboratory results
Grade 4 (> 20 x ULN)	Permanently discontinue pamiparib
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF > 500 msec or Change in QTc interval > 60 msec from the highest value at baseline or predose	• Obtain triplicate electrocardiograms (2 to 3 minutes apart) ~1 hour after initial electrocardiogram • If mean QTcF > 500 ms or mean change in QTc interval > 60 msec, hold pamiparib until evaluation of electrocardiograms by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal electrocardiogram • If mean QTcF > 500 ms or mean change in QTc interval > 60 msec is confirmed by cardiologist, permanently discontinue pamiparib

Table 4: Criteria for Modification of Pamiparib Dosing for Related Adverse Events (Continued)

Toxicity	Recommended Dose Modification[a]
Cardiac - General	
Grade 3	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level In the event of acute coronary syndrome, congestive heart failure and myocardial infarction, treatment should be permanently discontinued
Grade 4	Permanently discontinue pamiparib
Other adverse events	
Grade 3	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4	Permanently discontinue pamiparib

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; QTcF, QT interval corrected for heart rate using Fridericia's formula; ULN, upper limit of normal.

[a] Dosing of pamiparib can be withheld for up to 28 days consecutively.

6.1.5. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient.

The investigator and/or study personnel will keep accurate records of the quantities of capsules dispensed and used by each patient. This information must be captured in the source document at the end of each cycle. The investigator is responsible for pamiparib accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain pamiparib accountability records throughout the course of the study. This person will document the amount of pamiparib received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

6.1.6. Disposal and Destruction

At times throughout the study, all unused pamiparib will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.2. Concomitant Medications and Nondrug Therapies

6.2.1. Permitted Medications and Supportive Care

All treatments and supportive care, including antiemetic therapy, hematopoietic growth factors, and/or red blood cell/platelet transfusions, that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the local standards of medical care.

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluid supplementation, taken by or administered to the patient within 28 days before Day 1 and 30 days after the last dose of pamiparib will be recorded.

6.2.2. Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including chemotherapy, hormonal therapy, biologic therapy, radionuclide therapy, immunotherapy, investigational agent, Chinese anticancer medicine, or herbal remedies ≤ 5 half-lives if the half-life is known, ≤ 14 days if not known, before Day 1 and during the study. In addition, patients are not allowed to receive radiotherapy ≤ 21 days (≤ 14 days, if a single fraction of radiotherapy) before Day 1 and during the study. Bisphosphonate and denosumab use is permitted if the patient had already been receiving it at a stable dose ≥ 28 days before Day 1.

The primary metabolic pathway for pamiparib involves the CYP3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. Please refer to the drugs/substances listed in Appendix 6. Consumption of grapefruit and Seville oranges or their juices are not allowed throughout the study. No other dietary restrictions will apply.

6.2.3. Medications to Be Used with Caution

Based on preliminary in vitro screening assays, pamiparib is not a strong inhibitor of other human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Investigators need to be aware that pamiparib has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C9 and follow the prescribing information recommendations for use with CYP2C9 inhibitors. Therefore, careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Examples of these medications are listed in Appendix 7 and these should be used cautiously with drug concentration monitoring where appropriate.

In addition to CYP3A, pamiparib can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. See Appendix 7 for medications that should be used with caution for that reason.

7. STUDY ASSESSMENTS

7.1. Study Flow and Visit Schedule

The study-specific assessments and procedures with allowed time windows are outlined in Appendix 1. Assessments of efficacy will occur as outlined in Section 7.3. Assessments of safety will be based on AE monitoring and reporting (including attribution of AEs and SAEs), physical examinations, vital signs, ECGs, and clinical laboratory tests as outlined in Section 7.4.

7.2. Patient Demographics and Other Baseline Characteristics

7.2.1. Demographics

Demographic data will include gender, year of birth (or age), and race/ethnicity.

7.2.2. Medical History

Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) that were present before signing the ICF and considered relevant for the patient's study eligibility will be collected and captured. Clinically significant is defined as any events, diagnoses, or laboratory values that require treatment or follow-up, or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

For cancer history, the date of initial diagnosis and current disease status, staging, sites of disease, smoking history, prior anticancer therapies and dates administered, responses, and DOR to these treatments will also be recorded.

7.2.3. Other Baseline Characteristics

Information will also be collected regarding smoking history, prior medications/significant nondrug therapies, childbearing potential (Appendix 4), and any other assessments that are performed for the purpose of eligibility for inclusion in the study (Section 5), such as physical examination, vital signs, hematology, chemistry, and ECG.

7.3. Efficacy

7.3.1. Tumor Assessments

Following the screening tumor assessment, tumor assessments will occur at the schedule of every 8 weeks (±7 days) after Day 1 for 24 weeks, then every 12 weeks (± 7 days). Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response and DOR will be assessed by the investigator using PCWG3 criteria (Appendix 10).

The same imaging method(s) used at screening must be used throughout the study. Computed tomography (CT) scan with intravenous contrast and magnetic resonance imaging (MRI) are the preferred imaging methods. A documented standard-of-care tumor assessment may be used as the screening assessment provided it meets the requirements (Section 7.3.1.2).

All screening and on-study radiographs will be collected centrally so that review of the radiographs by an IRC may be performed. Instructions for submission of the radiographs will be provided in the study manual.

7.3.1.1. Determination of Eligibility

The investigator and study center radiologist will review tumor assessments to determine whether the patient has progression of soft tissue disease by modified RECIST Version 1.1 or PCWG3 criteria.

7.3.1.2. Screening Tumor Assessment

The baseline tumor assessment should include the following:

- Diagnostic-quality, contrast-enhanced CT scans of chest, abdomen, and pelvis
  - To be suitable for RECIST Version 1.1 assessments, CT scans should have a maximum thickness of 5 mm and no gaps.
  - CT is the preferred imaging method for tumor assessments of chest, abdomen, and pelvis.
  - If a positron-emission tomography/CT scan is performed, the CT portion should meet the CT scan requirements described above.
  - In patients for whom the preferred CT scans are contraindicated because of, for example, a CT intravenous contrast allergy, a CT of the chest without contrast and MRI of the abdomen and pelvis with contrast are recommended.
  - MRI scans may be performed in lieu of CT scans. At screening, tumor assessments should include a diagnostic quality, contrast-enhanced MRI scan of chest, abdomen, and pelvis. To be suitable for RECIST Version 1.1 assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps.
- Whole-body radionuclide bone scan to evaluate for bone metastases
- CT scan of the neck, if clinically indicated
  - Only to be performed at screening if the patient has known or suspected metastases in this area
  - MRI scan of the neck may be substituted for CT scan of the neck.
- MRI scan of the brain, if clinically indicated
  - Only to be performed at screening if the patient has symptoms that could be due to brain metastases
  - MRI is the preferred imaging method for tumor assessments of the brain.
  - In patients for whom MRI of the brain is not available or who are claustrophobic, a CT scan of the brain with intravenous contrast may be performed.

If brain metastases are present at baseline, the patient is eligible for this study if criteria listed under Exclusion Criterion 8 (Section 4.2) are met.

7.3.1.3. On-Study Tumor Assessments

All target and nontarget lesions must be assessed with the same imaging method used at baseline.

- Diagnostic-quality, contrast-enhanced CT scans of chest, abdomen, and pelvis (every 8 weeks ± 7 days for 24 weeks, then every 12 weeks ± 7 days)
  - CT scan with intravenous contrast is preferred, but the imaging method used at screening determines the imaging method of subsequent tumor assessments and must be used.
- Imaging of all other known sites of disease (every 8 weeks ± 7 days for 24 weeks, then every 12 weeks ± 7 days)

In addition to the protocol-specified tumor assessments, CT scans or other imaging studies may be performed at the investigator's discretion at any time as clinically indicated.

7.3.2. Prostate-Specific Antigen

PSA levels will be collected at timepoints specified in Appendix 1 and tested in a certified local laboratory. In addition, at least, the 3 most recent PSA levels before Day 1 (≥ 1 week between determinations) must be provided to document PSA progression before study entry.

Increases and decreases in PSA will be tracked to assess PSA responses as defined by the PCWG3 criteria described in Appendix 10. A PSA response or progression must be confirmed ≥ 3 weeks later.

7.3.3. Survival Assessments

Survival status of patients will be monitored through all phases of the study as outlined in Section 5 and Appendix 1. The date and cause of death will be recorded.

7.3.4. Quality-of-Life Assessments

Patients will complete all questionnaires in the clinic before any other study activities occur at timepoints specified in Appendix 1. Patients should be given sufficient instruction, space, time, and privacy for completion of the questionnaires. A study center team member should check for completeness of answers and encourage the patient to complete any missing answers. The questionnaires are validated instruments to measure the health status of patients (EQ-5D-5L; Appendix 8) and the quality of life of cancer patients (BPI-SF [Appendix 9]).

7.4. Safety

7.4.1. Adverse Events

Safety assessments should be performed at the study center visits indicated in Appendix 1.

All AEs and SAEs, regardless of their relationship to pamiparib, will be collected in the fashion and for the time periods outlined in Section 9. The regulatory definition of AEs and requirements for SAE reporting are outlined in Section 9.

7.4.2. Physical Examination, Vital Signs, ECOG Performance Status, Weight, and Height

A complete or limited physical examination, vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal, tympanic, or armpit temperature), weight, height, and ECOG performance status will be performed at timepoints specified in Appendix 1.

A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, cardiovascular status, and neurologic status. A limited physical examination should be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

ECOG performance status will be graded as outlined in Appendix 3.

7.4.3. Electrocardiograms

Single 12-lead ECGs with assessment of PR interval, QRS duration, and QT interval corrected for heart rate using Fridericia's formula will be obtained at timepoints specified in Appendix 1. Additional ECGs will be performed if clinically indicated. To minimize postural variability, it is important that patients are resting and in a semirecumbent or supine position for ≥ 5 minutes before each ECG collection. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability because of the effects of physiologic stress. Screening ECG must be performed within 14 days before Day 1. For the scheduled ECG assessment at the EOT Visit, ECG does not have to be repeated if it was performed within 14 days of the EOT Visit.

7.5. Safety Laboratory Assessments

On-study clinical laboratory evaluations starting from screening shall be performed by a central laboratory, as regionally available. An investigator may obtain safety laboratory results from their local laboratory as clinically indicated (eg, on the day of a patient's visit before results are available from the central laboratory for dose modifications or AE/SAE monitoring). Results from the central laboratory will serve as the official study laboratory result, where available. If required by local regulations, clinical laboratory evaluations performed by a local, instead of a central, laboratory are acceptable.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the study manual.

Laboratory assessments will be performed at the timepoints specified in Appendix 1 and may also be performed as clinically indicated. Laboratory assessments should be performed before pamiparib

administration. Screening blood tests must be performed within 14 days of Day 1. If tests were performed within 7 days of Day 1, they do not need to be repeated on Day 1.

7.5.1. Hematology

Hematology includes hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte count.

7.5.2. Chemistry

Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, chloride, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and total protein.

7.5.3. Urinalysis

Urinalysis includes blood, glucose, ketones, protein, red blood cells, and white blood cells.

7.5.4. Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening and as clinically indicated and will include HBV/hepatitis C virus (HCV) serology (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

7.6. Circulating Tumor Cell Count

Blood samples for CTC enumeration will be collected from patients at the timepoints specified in Appendix 1.

7.7. Pharmacokinetics

PK samples for pamiparib will be collected at all non-China centers and at centers with such capability in China. PK samples will be collected from patients at the following timepoints (Appendix 1): predose (within 30 minutes before dose) and 2 hours (± 30 minutes) postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The time of pamiparib administration on the day before Day 15 (Cycle 1 Day 14) must be recorded on the eCRF. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the laboratory manual.

7.8. Biomarkers

Blood samples for biomarker testing will be collected from patients at the timepoints specified in Appendix 1. A blood sample must be collected for prospective testing of CTC-HRD status during pre-screening or screening. Pre-screening for prospective testing of CTC-HRD status (blood sample) can be completed before the study eligibility screening. A separate pre-screening informed consent must be obtained.

An archived, formalin-fixed, paraffin-embedded tumor sample will be collected from patients, if available, for retrospective analysis of HRD mutational status. Archival tumor tissue shall be sent to the central laboratory for biomarker testing (either a formalin-fixed, paraffin-embedded block with tumor tissue [preferred] or approximately 10 unstained slides). The most recent tumor block is preferred.

In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is highly recommended. Written patient consent is required for fresh tumor biopsies. Optional biopsy will also be taken, if agreeable, at the EOT Visit for patients who have confirmed PD during the study from accessible tumor sites to obtain samples to explore resistance mechanisms. If feasible, any follow-up biopsy should, ideally, be taken from the same tumor lesion as the baseline biopsy.

Patients will also provide blood samples to be processed into plasma and cell fractions for the analysis of genetic defects associated with prostate cancer including but not limited to HRD signatures, DNA repair deficiency, and confirmation of BRCA1/2 mutational status.

Instructions for the processing, storage, and shipping of samples will be provided in the study manual.

7.9. Appropriateness of Measurements

All efficacy and safety assessments used in this study are standard and generally recognized as reliable, accurate, and relevant.

8. DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Study center audits may be made periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

8.1. Data Collection

Data will be entered into the eCRFs in an electronic data capture (EDC) system.

Data collection on the eCRF must follow the instructions described in the eCRF completion guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene, Ltd. (hereafter referred to as BeiGene) and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

8.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file, which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and any data being entered into the system for any subjects.

During the course of the study, a study monitor will make study center visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives the study drug, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

AEs will be coded using the Medical Dictionary for Regulatory Activities Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the Medical Dictionary for Regulatory Activities Version 20.0 or higher.

8.3. Quality Assurance

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to the facilities used for this trial and all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

9. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

9.1. Adverse Events

9.1.1. Definition and Reporting of an Adverse Event

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a pamiparib, whether considered related to pamiparib or not.

Examples of an AE include:

- Worsening of a chronic or intermittent preexisting condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after pamiparib administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either pamiparib or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

9.1.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 4.03 or higher.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to an AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas, seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.5.

9.1.3. Assessment of Causality

The investigator is obligated to assess the relationship between pamiparib and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to pamiparib will be considered and investigated. The investigator should consult the Pamiparib Investigator's Brochure in the determination of his/her assessment. There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always provides an assessment of causality for every SAE before transmission of the SAE report/eCRF to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality based on follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is at least "a reasonable possibility" that the AE may have been caused by pamiparib (ie, there are facts, evidence, or arguments to suggest possible causation, or a causal relationship between the AE and the drug cannot be ruled out). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of pamiparib/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of pamiparib
- Biologic plausibility

An AE should be considered "related" to pamiparib if any of the following are met, otherwise the event should be assessed as "not related":

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of pamiparib). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).
- A causal relationship between the AE and the study drug cannot be ruled out

9.1.4. Follow-Up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology if conducted.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE follow-up report/eCRF should be resent to the sponsor within the timeframes outlined in Section 9.5.1.

9.1.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, hematology, or coagulation) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is entrusted to the judgment of the investigator. In general, these are the abnormalities that:

- Are associated with clinical signs or symptoms, or

- Require active medical intervention, or
- Lead to dose interruption or discontinuation, or
- Require close observation, more frequent follow-up assessments, or
- Further diagnostic investigation

9.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it was more severe.

- Requires hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in disability/incapacity

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.3. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.3.1. Adverse Event Reporting Period

After the ICF has been signed, but before initiation of pamiparib, only SAEs should be reported to the sponsor.

After initiation of treatment, all AEs and SAEs, regardless of relationship to treatment, will be reported until 30 days after the last dose of pamiparib or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

After a patient is discontinued from the study, investigators are not obligated to actively seek AEs or SAEs from the former patients. However, if the investigator learns of any SAE, including a death, at any time, and considers the SAE related to pamiparib, the investigator will notify the sponsor.

9.3.2. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.4. Study-Specific Adverse Event and Serious Adverse Event Reporting Instructions

9.4.1. Disease Progression

"Disease progression" (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an event term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the event terms.

For example, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a patient experienced a fatal multiorgan failure due to disease progression, the term "multiorgan failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression".

9.4.2. Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death", "death of unknown cause", or "death unexplained".

9.5. Prompt Reporting of Serious Adverse Events

9.5.1. Timeframes for Submitting Serious Adverse Events

SAEs will be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 5: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial SAE Report	Document	Follow-up SAE and AE of Special Interest Report	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	Email or fax SAE form or Pregnancy form

Abbreviations: AE, adverse event; SAE, serious adverse event.

9.5.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.5.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.3.

The sponsor will provide contact information for SAE receipt.

9.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 9.6) will be submitted to all applicable regulatory authorities and investigators for pamiparib studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

9.6. Suspected Unexpected Serious Adverse Reactions and Expedited Reporting

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information in the Investigator's Brochure) and assessed as related to pamiparib either by the investigator or the sponsor. The sponsor will promptly assess the expectedness for all SAEs against the list of expected serious adverse reactions in the Reference Safety Information and expeditiously submit suspected unexpected serious adverse reactions to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

9.7. Pregnancy Reporting

If the partner of a patient becomes pregnant while receiving pamiparib or within 6 months after completion of the last dose of pamiparib, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to pamiparib should be recorded and reported as an SAE.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Details of the statistical analyses will be included in the Statistical Analysis Plan.

10.1. Analysis Sets

- Safety Analysis Set: includes all patients enrolled into the study who receive any dose of pamiparib. The Safety Analysis Set will be used for all safety analyses.
- Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1 of Table 2): includes all patients in the Safety Analysis Set who had measurable disease at baseline and at least 1 postbaseline tumor assessment, unless they permanently discontinue pamiparib or the study early due to clinical progression or death before tumor assessment. The Efficacy-Evaluable Analysis Set is the primary analysis set for tumor response analysis.
- PSA-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2 of Table 2): includes all patients in the Safety Analysis Set as per Inclusion Criterion 7 at baseline (≥ 3 rising

PSA levels with ≥ 1 week between determinations and screening PSA ≥ 2 μg/L) and who had at least 1 postbaseline PSA measurement, unless they permanently discontinue pamiparib or the study early due to clinical progression or death before completed PSA assessment.

- PK Analysis Set: includes all patients who received pamiparib and for whom valid pamiparib PK parameters can be estimated.

10.2. Efficacy Analyses

10.2.1. Primary Efficacy Endpoint Analyses

The primary endpoints of the study include ORR by IRC assessment in CTC-HRD-positive patients with measurable disease and PSA response rate in CTC-HRD-positive patients with or without measurable disease per PCWG3 criteria.

ORR is defined as the proportion of patients with best objective response of CR or PR confirmed at a subsequent timepoint ≥ 4 weeks later by IRC assessment. Patients without tumor assessment are considered non-responders.

ORR is assumed as 35% for pamiparib and estimated as 15% for historical control in the study population. The null and alternative hypotheses are set as follows:

H_0: ORR = 15%

H_a: ORR > 15%

PSA response rate is defined as the proportion of patients with PSA decline ≥ 50% from baseline (confirmed by a second PSA value ≥ 3 weeks later).

PSA response rate is assumed as 50% for pamiparib and estimated as 30% for historical control in the study population. The null and alternative hypotheses are set as follows:

H_0 : ORR = 30%

H_a : ORR > 30%

Binomial exact tests will be performed for above hypotheses in the Efficacy-Evaluable Analysis Set. Two-sided binomial exact 95% CI of response rate will be constructed to assess the prevision of the estimates.

To control the overall study type-I error rate, ORR and PSA response rate will be tested sequentially. If the ORR test shows significance at 1-sided 0.025 significance level, PSA response rate will be tested at a 1-sided 0.025 significance level.

The primary efficacy analyses will be conducted when mature response data have been observed, which will be determined by the sponsor.

A sensitivity analysis of response rate will be conducted using the Safety Analysis Set.

ORR and PSA response rate will be summarized in the specified subgroups: age group (< 65 versus ≥ 65), race, geographic region, ECOG performance status, BRCA1/2-mutant status, and number of prior lines of therapy.

10.2.2. Secondary Efficacy Endpoint Analyses

DOR by IRC assessment, ORR by investigator, and time to objective response and clinical benefit rate as assessed by investigator will be evaluated in patients with CTC-HRD-positive mCRPC with measurable disease per PCWG3 criteria.

Time to PSA response, duration of PSA response, time to PSA progression, time to SSE, rPFS by IRC, and OS will be evaluated in patients with CTC-HRD-positive mCRPC with or without measurable disease per PCWG3 criteria.

DOR is defined as the time from the date of the earliest documented confirmed response of CR or PR to radiographic disease progression by IRC or death due to any cause, whichever occurs first.

Time to objective response is defined as the time from the date of the first dose of study drug to the first documented confirmed response of CR or PR.

Clinical benefit rate is defined as the proportion of patients with a documented confirmed response of CR, PR, or stable disease.

Time to PSA response is defined as the time from the date of the first dose of study drug to the first documented confirmed PSA response.

Duration of PSA response is defined as the time from the date of the earliest documented confirmed PSA response to PSA progression or death due to any cause, whichever occurs first.

Time to PSA progression is defined as the time from the date of the first dose of study drug to a ≥ 25% increase in PSA with an absolute increase of ≥ 2 µg/L above the nadir (or above the baseline for patients with no PSA decline after 12 weeks), confirmed by a second value ≥ 3 weeks later.

Time to SSE is defined as the time from the date of the first dose of study drug to the first symptomatic fracture, radiation or surgery to bone, or spinal cord compression.

rPFS is defined as the time from the date of the first dose of study drug to radiographic disease progression by IRC or death due to any cause, whichever occurs first.

rPFS censoring rule will follow US Food and Drug Administration Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (FDA 2007). Data for patients without PD or death at the time of analysis will be censored at the date of the last tumor assessment. Data for patients who initiated new anticancer therapy will be censored at the last tumor assessment date before the introduction of new anticancer therapy. Data for patients who had 2 or more consecutive missed scheduled tumor assessments immediately before PD will be censored at the last tumor assessment date before the 2 missed tumor assessments. Further details will be described in the Statistical Analysis Plan.

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

Time-to-event variables of DOR, duration of PSA response, time to PSA progression, time to SSE, rPFS, and OS will be estimated using the Kaplan-Meier method. The median of these time-to-event variables will be presented along with their 2-sided 95% CI using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982).

Descriptive statistics will be provided for time to objective response and time to PSA response. Only responders will be included in analyses for DOR, duration of PSA response, time to response, and time to PSA response.

The ORR as assessed by investigator and its exact 2-sided 95% CI will be reported.

10.3. Pharmacokinetic Analyses

Pamiparib concentrations will be summarized by nominal time of collection. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Population PK analysis may be carried out to include plasma concentrations from this study in an existing model. Additional PK parameters such as apparent clearance (CL/F) of the drug from plasma and area under the plasma concentration-time curve from 0 to 12 hours postdose (AUC_{0-12}) may be derived from the population PK analysis if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results of the population PK and exposure-response analyses may be reported separately from the clinical study report.

10.4. Exploratory Analyses

[redacted]

10.5. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs. Laboratory values, vital signs, physical examinations, and ECG findings will also be used in determining the safety of the study treatment.

10.5.1. Extent of Exposure

Extent of exposure to pamiparib will be summarized descriptively as the duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (mg/day), and relative dose intensity.

The number (percentage) of patients requiring dose reductions, pamiparib holds, and permanent pamiparib discontinuation due to AEs will be summarized. Frequency of dose reductions and pamiparib withholding will be summarized by categories.

10.5.2. Adverse Events

The AE will be coded using Medical Dictionary for Regulatory Activities Version 20.0 or higher and graded using NCI-CTCAE Version 4.03 or higher.

A TEAE is defined as an AE that had an onset date on or after first dose of pamiparib or was worsening in severity from baseline (pretreatment) up to 30 days following permanent discontinuation of pamiparib or initiation of new anticancer therapy, whichever occurs first. All TEAEs will be included in summary tables and in-patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest grade according to NCI-CTCAE Version 4.03 or higher within a system organ class and preferred term, even if the patient experienced more than one TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study treatment. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAEs $\geq$ Grade 3, pamiparib-related TEAEs, and TEAEs that led to pamiparib withholding or permanent discontinuation will also be summarized.

10.5.3. Laboratory Analyses

Clinical laboratory (eg, hematology and chemistry) values to be evaluated will be specified in the Statistical Analysis Plan and collected in the EDC system. Collected values may be a subset of all the values obtained in the requested sampling, eg, a complete blood count with differential may be requested for the evaluation of neutrophils only. Analyzed laboratory values that are abnormal will be flagged and identified as outside (above or below) the normal range.

Laboratory parameters that are graded in NCI-CTCAE Version 4.03 or higher will be summarized by NCI-CTCAE grade. Shift tables will be provided as appropriate.

10.5.4. Physical Examinations

Physical examination results collected in association with an AE will be listed and summarized**.**

10.5.5. Vital Signs

Specific vital signs (eg, blood pressure and temperature) will be summarized and listed. The change from baseline will also be presented.

10.5.6. Electrocardiograms

The percentage of patients with abnormal and clinically significant ECG findings will be presented.

10.6. Sample Size Consideration

This study is designed to provide adequate power for primary endpoints of ORR and PSA response rate. A sample size of approximately 100 patients is planned (at approximately 45 centers with a projected average enrollment of 2 to 3 patients per center).

Assuming ORR of 35% for pamiparib in CTC-HRD-positive patients versus 15% for historical control in patients with measurable disease, the study power is 88% using a binomial exact test and 1-sided type-I error of 0.025 with n = 50. The binomial exact 95% CI of 35% ORR is 22.1% to 49.8% with a sample size of 50 patients.

Assuming PSA response rate of 50% for pamiparib versus 30% for historical control in CTC-HRD-positive patients with or without measurable disease, a sample size of 80 patients in this population will provide 95% study power using a binomial exact test and 1-sided type-I error of 0.025. The binomial exact 95% CI of 50% response rate is 38.6% to 61.4% with n = 80.

To explore the efficacy of pamiparib in patients with CTC-HRD-negative, but BRCA1/2-mutant mCRPC with or without measurable disease, approximately 20 patients will be enrolled in these cohorts.

10.7. Interim Analysis

A non-binding interim futility analysis will be performed among the first 20 patients enrolled in Cohorts 1 and 2 (Table 2). If the confirmed PSA response rate is < 30% (< 6 responses), enrollment will be halted and safety and efficacy data will be further evaluated before making the decision of stopping enrollment permanently. The decision to continue the enrollment may be made at any time the 6 confirmed PSA responses in Cohorts 1 and 2 can be documented; enrollment of all 20 patients is not required before determining further patient accrual.

11. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

11.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to appropriate regulatory agency before the study is initiated at a study center in that country.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Council for Harmonisation guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 Code of Federal Regulations, Part 50, and 21 Code of Federal Regulations, Part 56, are adhered to. In addition, this clinical study will be conducted

in the European Union according to Directive 2001/20/EC, until the application of Regulation EU No 536/2014, which will then be followed.

Investigators and all subinvestigators must provide documentation of their financial interest or arrangements with BeiGene or proprietary interests in the drug being studied. This documentation must be provided before the participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify BeiGene or its authorized representative of any change in reportable interests during the study and for 1 year following completion of the study.

11.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted by the principal investigator and the study center in accordance with Good Clinical Practice and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's ICF, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IEC/IRB.

The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study.

Before pamiparib can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the ICF, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IEC/IRB approval of the amended form before new patient consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended ICF/other information, the approved amended ICF/other information and all related correspondence must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.2.4. Investigator Reporting Requirements

As indicated in Section 9.5, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the USA, a study center-specific HIPAA consent may be used). The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, year of birth, and an identification code (ie, not names) should be recorded on any form or biologic sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from BeiGene, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the Investigational New Drug application, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

11.2.6. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. This also applies to records for those patients who discontinue the study early. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRFs exist within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before the study start and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes

tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data on CD-ROMs for archiving the data at the study center.

11.2.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused pamiparib. This includes acknowledgment of receipt of each shipment of pamiparib (quantity and condition), patient dispensing records, and returned or destroyed pamiparib. Dispensing records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the study center's standard operating procedure for pamiparib disposal/destruction to ensure that it complies with BeiGene requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study, following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused pamiparib supplies, including empty containers, according to these procedures. If the study center cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the study center and BeiGene or its representative for destruction or return of unused pamiparib supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.2.8. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.9. Protocol Adherence

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert that they will apply due diligence to avoid protocol deviations.

11.3. Sponsor Responsibilities

11.3.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities and the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. As applicable by local requirements, written documentation of regulatory authorities, IRB/IEC, and required study center approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming his/her willingness to remain in the study.

11.3.2. Use of Information and Publication

A clinical study report will be prepared and provided to the regulatory agency(ies) of participating countries. The sponsor will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The sponsor recognizes the importance of communicating medical study data, and therefore, encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the clinical study agreement.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement, is executed, that contract's publication provisions shall apply rather than this statement.

11.4. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused pamiparib
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including but not limited to safety or ethical issues or severe noncompliance with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable

regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused pamiparib in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

11.5. Records Retention and Study Files

11.5.1. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, or electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure that there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the timeperiod for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including but not limited to the following: archiving at an off-site facility and transfer of ownership of or responsibility for the records in the event that the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study center for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the study center so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Biologic samples at the conclusion of this study may be retained in storage by the sponsor as outlined in the study manual.

11.5.2. Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

In addition, details of the pamiparib assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

The sponsor will not routinely inform the investigator or patient of the test results because the information generated from this study will be preliminary in nature and the significance and scientific validity of the results will be undetermined at such an early stage of research.

11.6. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel

- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 11.3.2.

If a written contract for the conduct of the study that includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

11.7. Joint Investigator/Sponsor Responsibilities

11.7.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation Good Clinical Practice guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.7.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.7.3 Publication Policy

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

After conclusion of the study and without prior written approval from BeiGene, investigators in this

study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for the earlier of: at least 2 years or the period indicated in the clinical study agreement.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

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13. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Phase	**Pre-screening[a]**	**Screening[a]**	**Treatment[b]**					**Un-scheduled Visit[c]**	**End-of-Treatment (EOT) Visit[d]**	**Safety Follow-up[e]**	**Long-term Follow-up[f]**
Day of Phase	**≤ 28**	**-28 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**				
			Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**				
Allowed time window				± 2	± 3	± 3	± 5				
Study Day	≤ 28	-28 to -1	1	15	29	43	57, 85, etc.	Varies	Varies	Varies	Varies
Informed consent	X	X									
Eligibility criteria		X									
Demographics, medical history, smoking history		X									
Complete physical examination		X							X		
Limited physical examination			X	X	X	X	X	X			
Vital signs and weight[g]		X	X	X	X	X	X	X	X		
Height		X									
ECOG performance status		X	X		X		X	X	X		
12-lead ECG[h]		X (-14 to -1)	X	X	X	X	X	X	X		
Hematology[i]		X (-14 to -1)	X	X	X	X	X	X	X	X	
Chemistry[i]		X (-14 to -1)	X	X	X	X	X	X	X	X	
Urinalysis[i]		X (-14 to -1)	X					X	X		
HBV/HCV tests[j]		X	As clinically indicated								
BPI-SF and EQ-5D-5L questionnaires			X		X		X		X		
PSA levels[k]		X	X		X		X (q4w ± 7d)	X	X		X (q4w ± 7d)
Testosterone[w]	X	X							X		

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Study Phase	**Pre-screening[a]**	**Screening[a]**	**Treatment[b]**					**Un-scheduled Visit[c]**	**End-of-Treatment (EOT) Visit[d]**	**Safety Follow-up[e]**	**Long-term Follow-up[f]**
Day of Phase	**≤ 28**	**-28 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**				
			Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**				
Allowed time window				± 2	± 3	± 3	± 5				
Study Day	≤ 28	-28 to -1	1	15	29	43	57, 85, etc.	Varies	Varies	Varies	Varies
CT with intravenous contrast of chest, abdomen and pelvis[l]		X					X (q8w ± 7d for 24 weeks, then q12w ± 7d)	X	X		X (~q12w)
Bone scan[m]		X					X (q8w ± 7d for 24 weeks, then q12w ± 7d)	X	X		X (~q12w)
MRI scan of brain, if clinically indicated[n]		X						X			
Patient treatment authorization		X[a]									
Pamiparib			Twice a day dosing continuously								
Pamiparib dispensing/accountability			X		X		X	X	X		
Adverse events[o]		X	X	X	X	X	X	X	X	X	X
Concomitant medication(s)[p]		X	X	X	X	X	X	X	X	X	X (~q12w)
Pharmacokinetics[q]			X	X							
Blood sample for CTCs[r]	X	X	X				X (q8w ± 7d for 24 weeks, then q12w ± 7d)		X		

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Study Phase	**Pre-screening[a]**	**Screening[a]**	**Treatment[b]**					**Un-scheduled Visit[c]**	**End-of-Treatment (EOT) Visit[d]**	**Safety Follow-up[e]**	**Long-term Follow-up[f]**
Day of Phase	**≤ 28**	**-28 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**				
			Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**				
Allowed time window				± 2	± 3	± 3	± 5				
Study Day	≤ 28	-28 to -1	1	15	29	43	57, 85, etc.	Varies	Varies	Varies	Varies
Blood sample for biomarkers[s]			X				X (q8w ± 7d for 24 weeks, then q12w ± 7d)		X		
Archival tumor tissue[t]		X									
Fresh tumor tissue (additional consent required)[u]		X							X		
Survival follow-up[v]											X (~q12w)

Abbreviations: -7/-14/-28 to -1, Day -7/-14/-28 to Day -1 of screening; AE, adverse event; BPI-SF, Brief Pain Inventory Short Form; CT, computed tomography; CTC, circulating tumor cell; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, End-of-Treatment; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire; HBV, hepatitis B virus; HCV, hepatitis C virus; HRD, homologous recombination deficiency; MRI, magnetic resonance imaging; PARP, poly (ADP-ribose) polymerase; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PD, progressive disease; PK, pharmacokinetic; PSA, prostate-specific antigen; q4w ± 7d, every 4 weeks ±7 days; q8w ± 7d, every 8 weeks ±7 days; ~q12w, approximately every 12 weeks; SAE, serious adverse event.

a. Pre-screening for prospective testing of CTC-HRD status (blood sample) can be completed before the study eligibility screening. A separate pre-screening informed consent must be obtained. Screening must occur within 28 days before Day 1. Some assessments have a narrower screening window as shown in the table. Assessments obtained within 7 days of Day 1 do not have to be repeated on Day 1. Patient treatment authorization may occur as late as Day 1 before the first dose of pamiparib.

b. Patients must initiate study treatment within 4 days after authorization for treatment. Administration of pamiparib will continue until PD, as assessed by investigator per PCWG3 criteria, unacceptable toxicity, death, or another discontinuation criterion is met (Sections 5.5.1 and 5.6.4. A cycle is 28 days. Assessments shown for Cycle 3 apply to all subsequent cycles, unless noted otherwise.

c. Unscheduled visits may occur at any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow-up of AEs. Study assessments of an unscheduled visit, as indicated by 'X,' should be performed based on the reason for the unscheduled visit. If PD is suspected, imaging studies should be performed and blood for biomarkers should be obtained as appropriate.

d. The EOT Visit should occur within 7 days after pamiparib has been permanently discontinued. A visit should be scheduled as soon as possible, but the EOT Visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which tumor assessments showed PD may be used as the EOT Visit if all required assessments were performed. Tumor assessments do not have to be repeated if they were performed within 14 days of the EOT Visit or at a prior response evaluation that documented PD. An ECG does not have to be repeated if it was performed within 14 days of the EOT Visit.

e. Approximately 30 days after the last dose of pamiparib or before initiation of new anticancer therapy, whichever occurs first, the Safety Follow-up Visit will occur with the outlined safety assessments. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit, (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible. For patients who do not want to or cannot return to the clinic for the Safety Follow-up Visit, the patient should be contacted by telephone for a review of AEs. If these attempts of contact are unsuccessful, the additional attempts detailed in Section 5.6.3 should be made.

f. Patients will be followed for survival and initiation of new anticancer therapy via telephone contact or other means (eg, clinic visit) approximately every 12 weeks.

   Patients who were permanently discontinued from pamiparib for reasons other than PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed with tumor and PSA assessments every 12 weeks and 4 weeks (±7 days), respectively, until PD or any other reason listed in Section 5.6.4, whichever occurs first. For efficacy assessments as per protocol, refer to Section 7.3. If the patient refuses to return for these PSA and tumor assessments or is unable to do so, every effort should be made to contact the patient by telephone to determine the patient's disease status and survival.

   Should attempts of telephone contact be unsuccessful, the additional attempts detailed in Section 5.6.3 should be made. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up.

g. Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal, tympanic, or armpit temperature) will be measured before pamiparib administration and approximately 15 minutes before each collection of PK blood samples, if applicable, during the treatment phase.

h. ECGs will be obtained approximately every 28 days and at each subsequent visit including EOT. Additional ECGs will be performed, if clinically indicated.

i. Hematology includes hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte count.

   Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, chloride, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and total protein.

   Urinalysis includes blood, glucose, ketones, protein, red blood cells, and white blood cells.

j. Testing will be performed by a central laboratory and/or the local laboratory at screening and as clinically indicated and will include HBV/HCV serology (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

k. PSA levels will be assessed during screening, on Day 1, and every 4 weeks (± 7 days), or as clinically indicated. Responses by PCWG3 criteria must be confirmed ≥ 3 weeks later. Patients without PD at the EOT Visit should be followed with PSA assessments every 4 weeks (± 7 days) during the long-term follow-up phase.

l. Following the screening tumor assessment, tumor assessments will occur at the schedule of every 8 weeks (±7 days) after Day 1 for the first 24 weeks, then at the schedule of every 12 weeks (± 7 days). Any measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. The same imaging method(s) used at screening must be used throughout the study. A documented standard-of-care tumor assessment may be used as the screening assessment provided it meets protocol requirements (Section 7.3.1.2). CT scan with intravenous contrast is the preferred imaging method for assessment of chest, abdomen, and pelvis. Other imaging methods are allowed as outlined in Section 7.3.1.2. Imaging of other areas of disease should be performed every 8 weeks ± 7 days for 24 weeks, then every 12 weeks ± 7 days. Patients without PD at the EOT Visit should be followed with tumor

assessments every 12 weeks (± 7 days) during the long-term follow-up phase.

m. Whole-body radionuclide bone scan must be performed at screening and will then occur at the schedule of every 8 weeks (± 7 days) after Day 1 for the first 24 weeks, then at the schedule of every 12 weeks (± 7 days). Patients without PD at the EOT Visit should be followed with bone scans every 12 weeks (± 7 days) during the long-term follow-up phase.

n. MRI scan of the brain to assess for brain metastases must be performed at screening if the patient has symptoms that could be due to brain metastases. CT scan with intravenous contrast is acceptable if MRI is not available or the patient is claustrophobic. If brain metastases are present at baseline, the patient is eligible for this study if criteria listed under Exclusion Criterion 8 are met.

o. AEs and laboratory safety measurements will be recorded at each study visit, graded per National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 or higher, and assessed as outlined in Section 9. After the informed consent form has been signed, but before initiation of pamiparib, only SAEs should be reported. After initiation of pamiparib, all AEs and SAEs, regardless of relationship to pamiparib, will be reported until 30 days after last dose of pamiparib or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to pamiparib.

p. All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last dose of pamiparib will be recorded. Concomitant medications include new anticancer therapy information acquired during the long-term follow-up phase.

q. PK samples for pamiparib will be collected at various timepoints at all non-China centers and at centers with such capability in China. PK samples will be collected from patients at the following timepoints: predose (within 30 minutes before dose) and 2 hours (± 30 minutes) postdose on Cycle 1 Day 1 and Cycle 1 Day 15. The time of pamiparib administration on the day before Day 15 must be recorded on the electronic case report form. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the laboratory manual.

r. One blood sample (10 mL) must be collected for prospective testing of CTC-HRD status and CTC enumeration during pre-screening or screening. Blood samples (10 mL each) will then be collected every 8 weeks (± 7 days) after Day 1 for the first 24 weeks, then at the schedule of every 12 weeks (± 7 days), as well as at the EOT Visit (unless they had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the study manual.

s. One blood sample (8 mL) must be collected before initiation of pamiparib on Day 1 of Cycle 1 for the assessment of BRCA1/2 germline mutations. Two blood samples (10 mL each) will be collected for the assessment of plasma biomarkers of PARP inhibitor response/resistance before pamiparib administration every 8 weeks (± 7 days) after Day 1 for the first 24 weeks, then at the schedule of every 12 weeks (± 7 days), as well as at the EOT Visit (unless they had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the study manual.

t. Archival tumor tissue, if available, shall be sent to the central laboratory testing for retrospective analysis of HRD mutational status.

u. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is highly recommended. Written patient consent is required for fresh tumor biopsies. Optional biopsy will also be taken, if agreeable, at the EOT Visit for patients who have confirmed PD during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow-up biopsy should, ideally, be taken from the same tumor lesion as the baseline biopsy.

v. Patients will be followed for survival via telephone contact approximately every 12 weeks or as further detailed in Sections 5.6.2 and 5.6.3.

w. Testosterone must be collected either at Pre-screening or at screening.

APPENDIX 2. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247 (Eisenhauer et al 2009).

DEFINITIONS

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by computed tomography (CT) scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum

diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the electronic case report form (eCRF) (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing nontarget lesions.

When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorine-18 [F-18]fluorodeoxyglucose (FDG)-PET (PET scanning with the tracer FDG) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-

PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable.

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Note: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'not evaluable (NE)' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions, cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where SD or PD are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the

requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

Note: The duration of response and SD as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 4. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL", "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)

    NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.

    Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential", "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are females who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as females meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)

- Postmenopausal, defined as:
    - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
    - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

APPENDIX 5. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 6. PROHIBITED MEDICATIONS

Strong and Moderate CYP3A Inhibitors and Strong CYP3A Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib
Food products: grapefruit and juice (*Citrus paradisi*), Seville orange and juice (*Citrus aurantium*)
Herbal medications: *Schisandra sphenanthera*
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

Data compiled from the United States Food and Drug Administration "Guidance for Industry, Drug Interaction Studies;"
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm from the Indiana University School of Medicine's "Clinically Relevant" Table
http://medicine.iupui.edu/flockhart/table.htm; from the University of Washington's Drug Interaction Database
www.druginteractioninfo.org

APPENDIX 7. MEDICATIONS TO BE USED WITH CAUTION

Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index

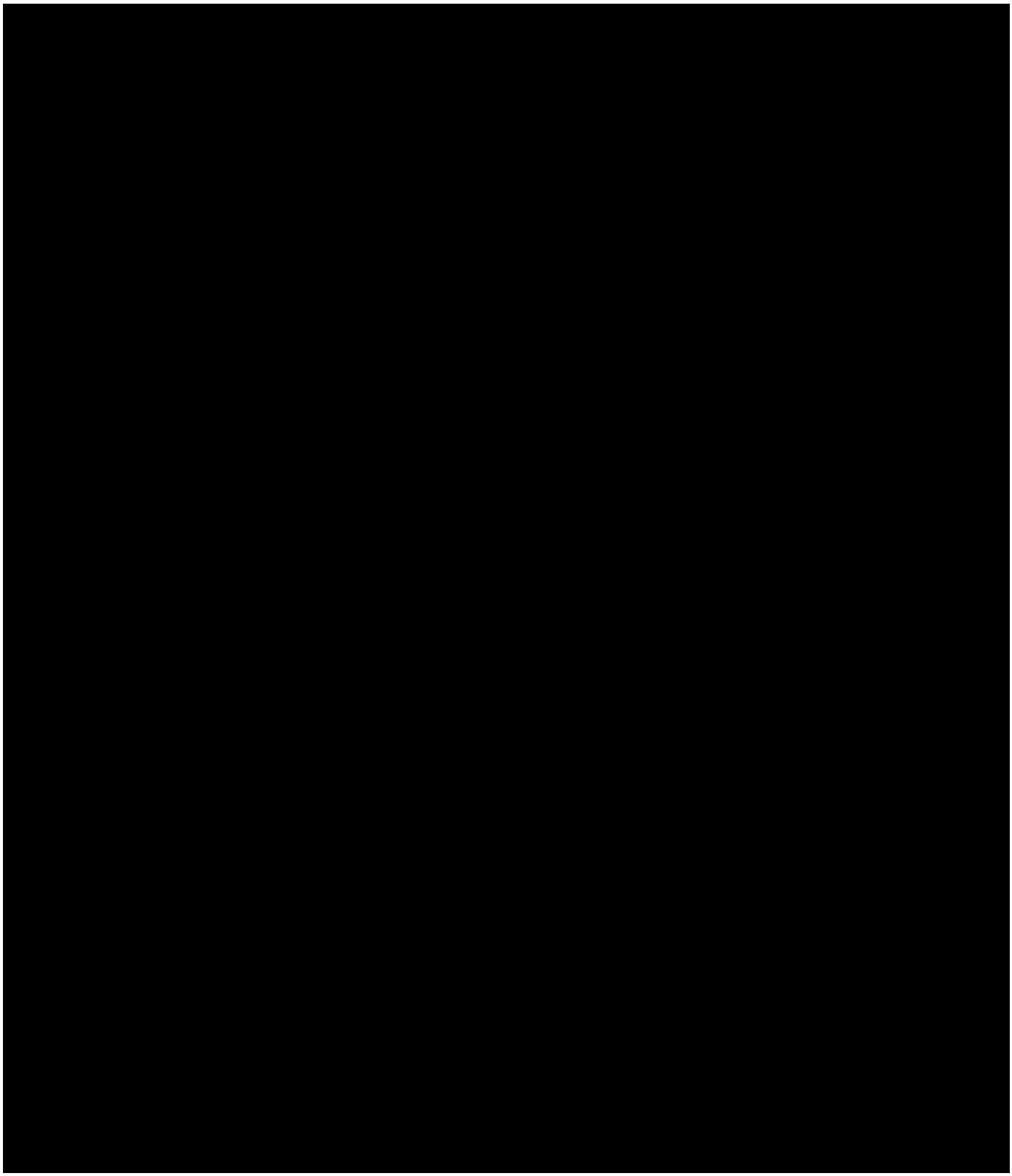
- Celecoxib[a]
- Phenytoin[b]
- Warfarin[b]

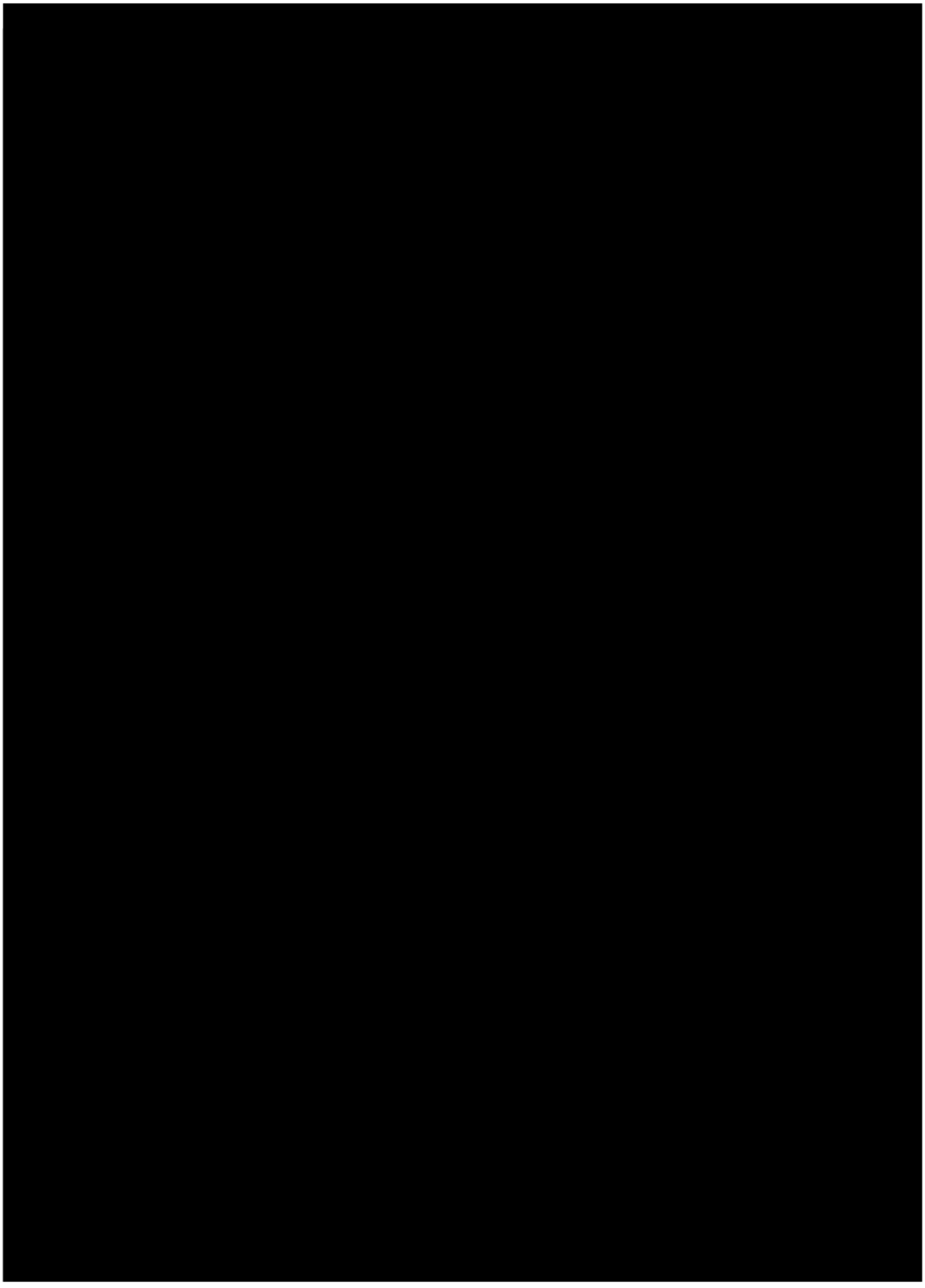
[a] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when coadministered with a known potent inhibitor, where AUCi is the AUC of the substrate when coadministered with a known potent inhibitor and AUC is the AUC of substrate alone.

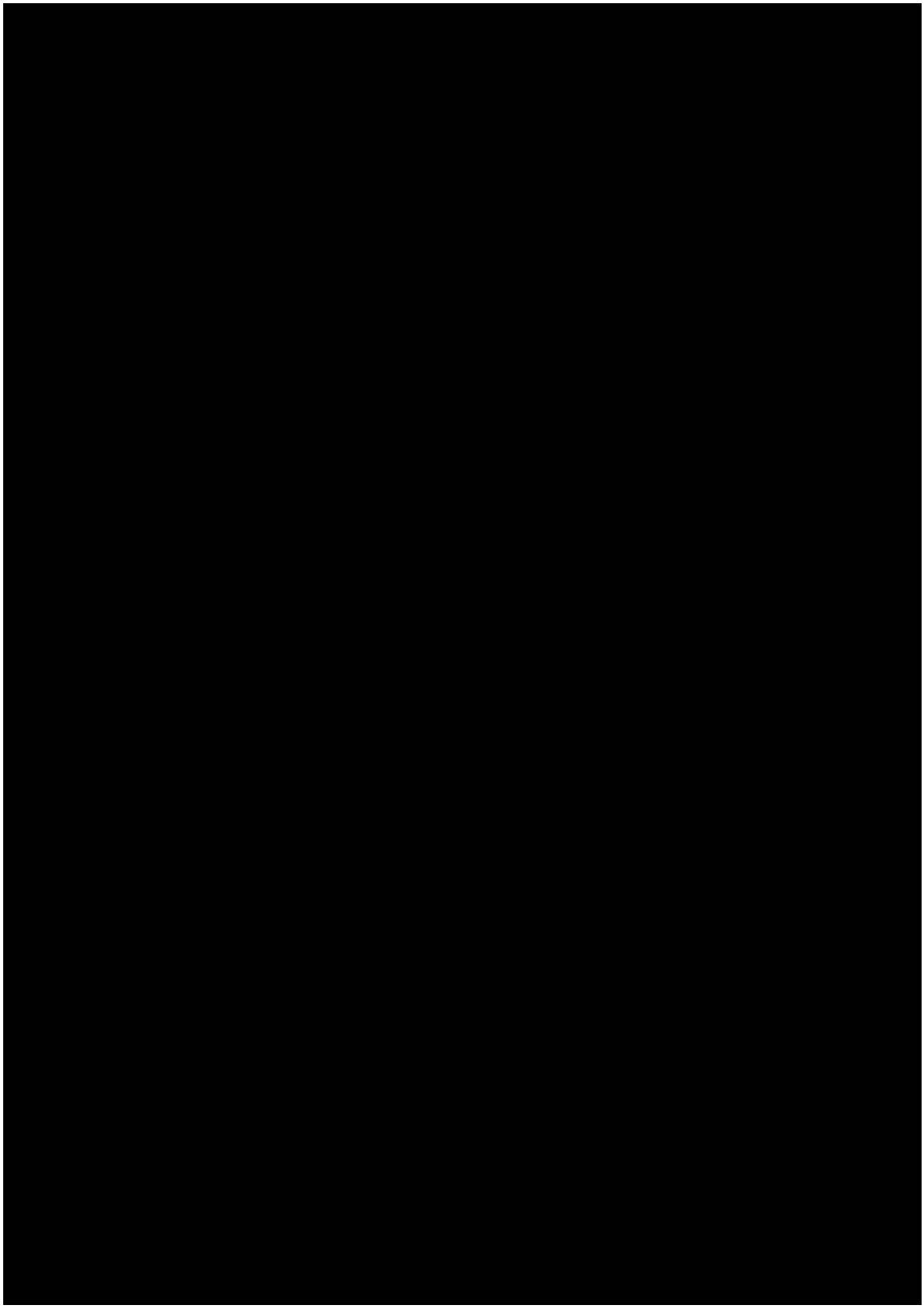
[b] Substrates with narrow therapeutic index: Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsade de Pointes).

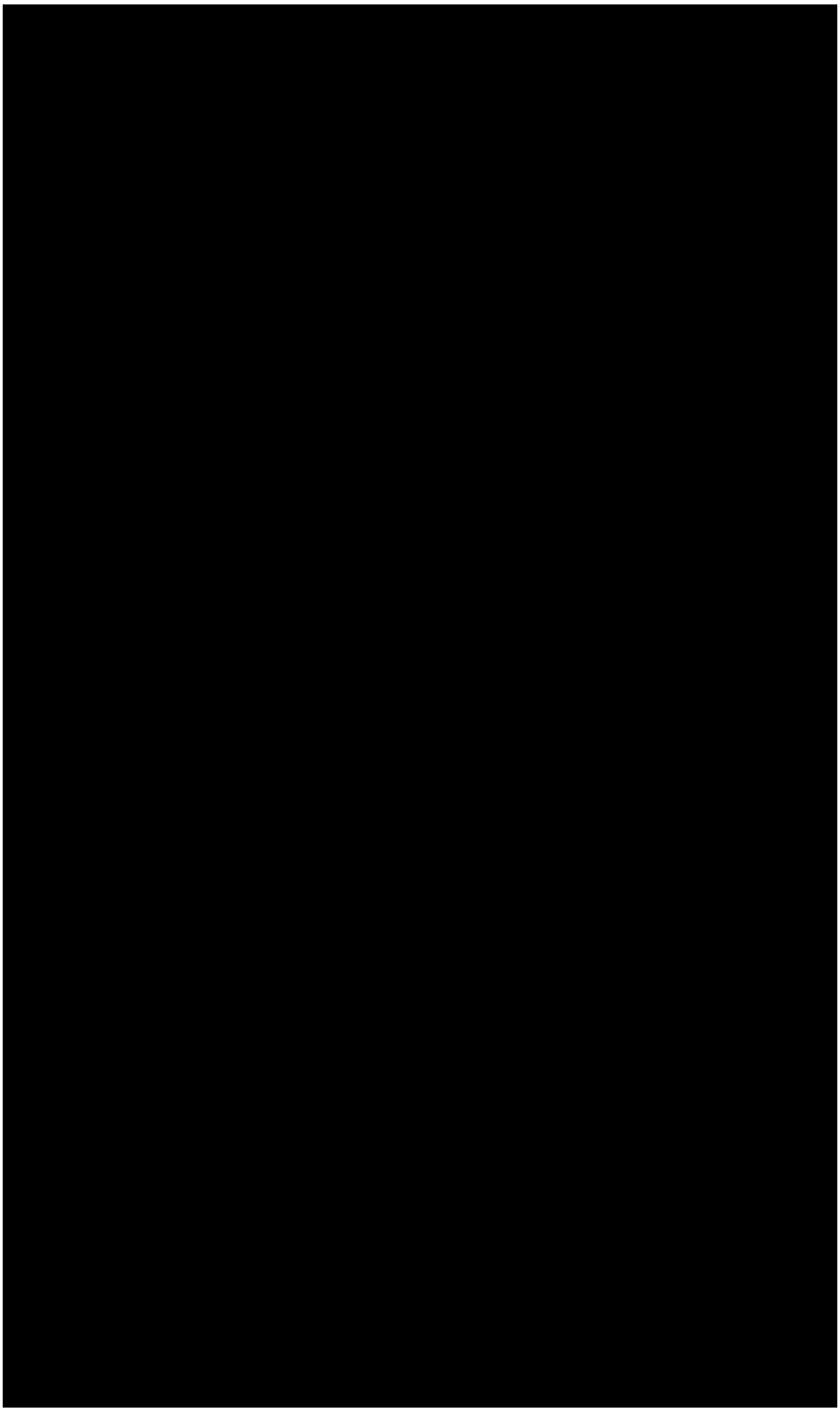
Strong CYP2C8 Inhibitors

- Gemfibrozil









APPENDIX 10. PROSTATE CANCER CLINICAL TRIALS WORKING GROUP 3

The information below was obtained from the following reference: Scher HI, Morris MJ, Stadler WM. Prostate Cancer Clinical Trials Working Group 3. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402-18 (Scher et al 2016).

Standard Baseline Disease Assessments Recommended by PCWG3

Assessment	PCWG3
Histology	Adenocarcinoma Adenocarcinoma with small-cell or neuroendocrine features Small-cell carcinoma Report Gleason sum for primary Consider rebiopsy of metastatic disease
Clinical	Age, pain, analgesic consumption, performance status, comorbidity assessment, history, and physical examination; prior local therapy; TNM stage at diagnosis; and PSA
Prior systemic treatment	Record each line of systemic therapy (single agent or combination) in order of administration, including start and stop dates, dose(s), and schedule(s), the disease state in which it was administered, and response (resistant versus sensitive) on the basis of PSA if appropriate Record type of progression on prior therapy (PSA, radiographic [bone, nodal, visceral], clinical [eg, pain escalation])
Prior radiation therapy	Site, administered dose per fraction, and treatment duration
Blood-based biomarkers	Host: CBC with differential, ALP, kidney/liver function, albumin, LDH, testosterone[a] Tumor: PSA and cPSA kinetics Optional: CEA, chromogranin A, neuron-specific enolase, CTC enumeration
Imaging Prostate/ prostate bed Nodal	Retained, cross-sectional imaging of prostate region if applicable CT or MRI: Nodes ≥ 1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic Record pelvic and extrapelvic (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to 5 nodes in total

Assessment	PCWG3
Visceral	Record new lesions versus growth of pre-existing lesions, and sites of new lesions CT or MRI: Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to five lesions per site Lesions ≥ 1.0 cm in the longest dimension are considered measurable Record new lesions versus growth of pre-existing lesions, and sites of new lesions
Bone	Record new lesions and sites of new lesions
Tumor profiling for determinants of prognostic, predictive, and resistance biomarkers	Consider rebiopsy of metastatic or locally recurrent lesion(s) for biologic characterization
Patient-reported outcomes	Pain assessment, opiate analgesia consumption, physical functioning (functional status), health-related quality of life; consider fatigue and PRO-CTCAE. Validated PRO instruments strongly recommended

Abbreviations: ALP, alkaline phosphatase; CBC, complete blood count; CEA, carcinoembryonic antigen; CNS, central nervous system; cPSA, complexed prostate-specific antigen; CT, computed tomography; CTC, circulating tumor cell; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PSA, prostate-specific antigen.

a. Ultrasensitive testosterone measures may be indicated where appropriate on the basis of drug under study and context.

Criteria for Progression at Trial Entry by Disease Manifestation

Variable	PCWG3
Blood-based	
PSA	Obtain sequence of rising values at a minimum of 1-week intervals 1.0 ng/mL is the minimal starting value if confirmed rise is only indication of progression unless pure small-cell carcinoma Estimate pretherapy PSADT if at least 3 values available ≥ 4 weeks apart
Imaging	
Nodes	Nodal progression sufficient for trial entry independent of PSA Measurable lesions not required for entry Modified RECIST 1.1 criteria, separate pelvic and extrapelvic disease, up to 5 nodal lesions total recorded

Variable	PCWG3
	Previously normal (< 1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed If the node progresses to ≥ 1.5 cm in the short axis, it is measurable; nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy, progression is defined per RECIST 1.1 Record presence of nodal and/or visceral disease separately Nodal sites: Locoregional: pelvic only Extrapelvic: retroperitoneal, mediastinal, thoracic, or other
Viscera	Visceral progression sufficient for trial entry independent of PSA, record separately by site of spread (lung, liver, adrenal, CNS); up to 5 lesions per site of spread Measurable lesions not required for entry Use RECIST to record visceral lesions as target or nontarget Record presence of nodal and/or visceral disease separately, Visceral sites: lung, liver, adrenal, CNS
Prostate/prostate bed (primary site)	Record prior treatment of primary tumor Perform directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence or absence of disease
Bone	Two new lesions Confirm ambiguous results by other imaging modalities (eg, CT or MRI), but only positivity on the bone scan defines metastatic disease to bone
Other sites of disease	Patients with treated epidural lesions and no other epidural progression are eligible
Type of progression at trial entry	Report separately: PSA only Bone only ± nodal disease Nodal disease only (no bone disease present) Visceral (lung, liver, adrenal, CNS) disease (± other sites) Record new lesions and site of new lesions versus growth of preexisting lesions, or both

Variable	PCWG3
Other markers Patient-reported outcomes	For pain palliation analyses, presence of clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) is a prerequisite; for pain progression analyses, patients may have any level of pain at baseline, including no pain
Abbreviations: CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, PSA doubling time; RECIST, Response Evaluation Criteria in Solid Tumors.	

Suggested Frequency of Assessment for Commonly Used Measures in Metastatic Prostate Cancer Clinical Trials

Assessment[a]	PCWG3
Clinical	
Symptoms/ performance status	Every cycle
Blood-based markers	
PSA	By cycle (every 3 or 4 weeks)
ALP, LDH	By cycle (every 3 or 4 weeks)
Serum chemistry, CBC	By cycle (every 3 or 4 weeks)
Circulating tumor cells	By cycle (every 3 to 4 weeks) if available
Imaging	
Bone scans	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks[b]
CT/MRI	Every 8 to 9 weeks for first 24 weeks, then every 12 weeks[b]
Patient-reported outcomes	By cycle (every 3 to 4 weeks)
Analgesic consumption (opioids/no opioids)	By cycle (every 3 to 4 weeks)

Abbreviations: ALP, alkaline phosphatase; CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PSA, prostate-specific antigen.

a. All measures should be assessed at baseline to determine changes over time.

b. There may be exceptions to these suggestions: in nonmetastatic castration-resistant prostate cancer trials, for example, imaging assessment intervals of 16 weeks are advised. Likewise, in long-term responders (> 2 to 3 years of clinical benefit and no signs of clinical or biomarker progression), reduced frequency of imaging is reasonable, such as every 16 to 24 weeks (4 to 6 months).

Suggested Outcome Measures for Clinical Trials in Metastatic Prostate Cancer: Report by Disease Manifestation

Assessment	PCWG3
Histology	Encourage rebiopsy of metastatic sites or local recurrence at progression to evaluate for histologic (ie, neuroendocrine/ small cell) transformation; in the context of clinical trials, encourage rebiopsy for biomarker assessment
Blood-based biomarkers	
PSA	Recognize that a favorable effect on PSA may be delayed for ≥ 12 weeks, even for a cytotoxic drug Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression Ignore early rises (before 12 weeks) in determining PSA response For control/relieve/eliminate endpoints: Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot, except with timing (8-9 or 12 weeks) depending on trial design Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL versus primary radiation therapy-treated patients who achieved a nadir less than 0.5 ng/mL Describe absolute changes in PSA over time from baseline to best response For delay/prevent endpoints (progression): After decline from baseline: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25% (standards for reporting PSA progression date may not indicate a need to stop treatment). Recording the duration of PSA decline of little value. Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present
CTC	Enumerate at the start of treatment: Record as favorable (4 or fewer cells per 7.5 mL of blood) or unfavorable (5 or more cells per 7.5 mL) If unfavorable, monitor for changes after treatment For control/relieve/eliminate endpoints: Report as change from unfavorable (5 or more cells per 7.5 mL of blood) to favorable (4 or fewer cells per 7.5 mL) and

Assessment	PCWG3
	separately, the percent change from baseline using a waterfall plot
	For delay/prevent endpoints: no validated definition exists (however, rising CTC counts are associated with a poor prognosis)
LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine N-telopeptide, hemoglobin, NLR	Descriptively report changes over time, may include the proportion showing normalization of a given biomarker and/or waterfall plots of percent change from baseline in a given biomarker
	Report institutional normal ranges to determine normalization of a given biomarker
Imaging biomarkers: nodal and visceral	
For control/relieve/eliminate endpoints	
General	Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately
	Record up to 5 lesions per site of disease
	Use RECIST 1.1 with caveats:
	Record changes in size using waterfall plot
	Confirm favorable change with second scan
	Record complete elimination of disease at any site separately
Nodes	Only report changes in lymph nodes that were ≥ 1.5 cm in the short axis
	Record changes in pelvic (regional) nodes versus extrapelvic (distant/metastatic) nodes separately
Visceral	Use RECIST 1.1 with caveats:
	Record changes in liver, lung, adrenal, and CNS separately
	Only report changes in lesions ≥ 1.0 cm in the longest dimension
For delay/prevent endpoints	General:
Nodal and visceral	Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately
	Use RECIST 1.1 but clearly record type of progression (growth of existing lesions versus development of new lesions) separately by site
	The recommendations apply to both nmCRPC and mCRPC
	Record up to 5 lesions per site of spread
	Report the proportion who have not progressed at fixed timepoints (6 or 12 months)
	Note that for some treatments, a lesion may increase in size before it decreases

Assessment	PCWG3
Nodal	Previously normal (< 1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1
Imaging biomarkers: bone Metastatic	For control/relieve/eliminate endpoints: Record changes as improved or stable (no new lesions) or worse (new lesions), with of resolved bone lesion Changes in intensity of uptake alone do not constitute progression or regression No new lesions: continue therapy in absence of other signs of progression New lesions (See Progression below) For delay/prevent endpoints (progression): Progression: Exclude pseudoprogression in the absence of symptoms or other signs of progression At least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan (2 + 2 rule) If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan Date of progression is the date of the scan that first documents the second lesion Changes in intensity of uptake alone do not constitute either progression or regression Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
nmCRPC	Nonmetastatic to metastatic progression: Any new unequivocal bone lesion, except if that lesion appears in the first post-treatment scan; in that case, document the event, continue treatment until 2 additional new lesions appear, and record both events
Patient-reported outcomes	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent timepoint (eg, a

Assessment	PCWG3
	30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use) For control/relieve/eliminate endpoints: Serial (eg, daily x 7 days) assessments at each timepoint can improve the stability of values Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement For delay/prevent endpoints: Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay endpoints; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use) Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later) Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire

Abbreviations: CNS, central nervous system; CTC, circulating tumor cell; HRQoL, health-related quality of life; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil/lymphocyte ratio; nmCRPC, nonmetastatic castration-resistant prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PRO, patient-reported outcome; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

APPENDIX 11. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1] and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable. Read more about creatinine standardization.

This CKD-EPI equation calculator should be used when Scr reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

GFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr /κ or 1, and

max indicates the maximum of Scr /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

APPENDIX 12. SIGNATURE OF INVESTIGATOR

Protocol Title: A Phase 2, Open-Label, Single-Arm Study of Pamiparib (BGB-290) for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) with Homologous Recombination Deficiency (HRD)

Protocol Identifier: BGB-290-202

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene, Ltd. or its designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____