STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-290-202
Study 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)
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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
HRQoL	Health-related quality of life
IC50	half-maximal inhibition concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Review Committee

Abbreviation	Definition
LDH	Lactate dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
MDRD STUDY EQ	Modification of Diet in Renal Disease study equation
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
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
PRO	patient-reported outcome
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
VAS	visual analog scale

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for protocol: 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). The focus of this SAP is for the planned analyses specified in the study protocol Version 1.0.

2 STUDY OVERVIEW

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 circulating tumor cells positive for homologous recombination deficiency per Epic Sciences assay (CTC-HRD-positive) (Cohorts 1 and 2) or deleterious germline or somatic mutation in BRCA1 or BRCA2 (Cohorts 3 and 4).

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 prostate-specific antigen (PSA) progression as per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria at time of study entry. The primary endpoints are objective response rate (ORR) by Independent Review Committee (IRC) for patients with measurable disease (Cohort 1, n ≈ 50) and PSA response rate for patients with or without measurable disease (Cohorts 1 and 2, n ≈ 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 (Cohort 1A) or negative/unknown BRCA1/2 mutation (Cohort 1B). Cohort 2 will include 30 mCRPC CTC-HRD positive patients with bone metastasis only and positive (Cohort 2A) or negative/unknown BRCA1/2 (Cohort 2B). 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 disease only, respectively (see Table 1).

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.

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

Safety assessments will occur on Day 1 and Day 15 of Cycles 1 and 2, on Day 1 of every cycle thereafter and as clinically indicated. 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 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 or higher. A Safety Monitoring Committee will periodically review safety data.

Pharmacokinetic (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 progressive disease (PD), unacceptable toxicity, death, or another discontinuation criterion is met. 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.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

- To evaluate the efficacy of pamiparib in patients with positive mCRPC for circulating tumor cells with homologous recombination deficiency (CTC-HRD-positive; per Epic Sciences assay), as per PCWG3 criteria

3.2 SECONDARY OBJECTIVES

- To further evaluate the efficacy of pamiparib in patients with CTC-HRD-positive mCRPC with measurable disease (Cohort 1 of 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 Table 1, respectively), as

per PCWG3 criteria

- To evaluate the safety and tolerability of pamiparib

3.3 EXPLORATORY OBJECTIVES

[redacted]

- [redacted]

4 STUDY ENDPOINTS

4.1 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 Table 1)
- 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 1, respectively)

4.2 SECONDARY ENDPOINTS

For Patients with CTC-HRD-Positive mCRPC with Measurable Disease (Cohort 1 of 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)

For Patients with CTC-HRD-Positive mCRPC with or without Measurable Disease (Cohorts 1 and 2 of 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)

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

- Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to NCI-CTCAE Version 4.03 or higher

4.3 EXPLORATORY ENDPOINTS

- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

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 binominal exact test and 1-sided type-I error of 0.025 with n = 50. The binominal 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 binominal exact test and 1-sided type-I error of 0.025. The binominal 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.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

- Safety Analysis Set (SAF): includes all patients enrolled in 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 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 prior to tumor assessment. A similar analysis population will exist for exploratory analyses of Cohort 3.
- Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2 of 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. A similar analysis population will exist for exploratory analyses of Cohorts 3 and 4.
- PK Analysis Set: includes all patients who received pamiparib and contributed at least one plasma concentration.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of study treatment. For assessments conducted on or after the date of the first dose of study treatment, study day will be calculated as (assessment date – date of first dose of study treatment + 1). For assessments conducted before the date of the first dose of study treatment, study day is calculated as (assessment date – date of first dose of study treatment). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix **Error! Reference source not found.**.

Treatment duration: The treatment duration will be calculated as (date of last dose of study treatment – date of first dose of study treatment + 1).

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected on or before the first dose date.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 decimal place.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Duration of imaging-based event endpoints (such as PFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 10.1.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

When summarizing categorical variables, patients with missing data are included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented.

When summarizing continuous variables, patients with missing data are not included in calculations. No imputations are made.

For the Health-related quality of life (HRQoL) questionnaires, the missing data will be handled in accordance with the scoring manual of each patient-reported outcome (PRO) questionnaire (Cleeland, 2009).

6.2.4 Multiplicity Adjustment

To control the overall study type I error rate, the primary efficacy endpoint analyses for ORR and PSA response rate will be tested sequentially.

If the hypothesis test for ORR is statistically significant at a one-sided 0.025 level (ie, one-sided p-value < 0.025), then the PSA response rate will be tested at a one-sided 0.025 significance level. If the primary endpoint of ORR is not statistically significant, the primary endpoint of PSA response rate will not be tested for statistical significance.

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The following patient disposition information will be summarized:

- Number of patients treated
- Number (%) of treated patients who discontinued from treatment
- Reason(s) for treatment discontinuation
- Number (%) of treated patients who remain on treatment
- Number (%) of treated patients who discontinued from study
- Reason(s) for study discontinuation
- Number (%) of treated patients who remain in study
- Treatment follow-up time: defined as the time from the first dose date to the end of treatment date for patients discontinued from the treatment, or the database cutoff date for ongoing patients.

- Study follow-up time: defined as the time from the first dose date to death date or end of study date (whichever occurred first) for patients who discontinued study or the data cutoff date for ongoing patients.

6.3.2 Protocol Deviations

Major protocol deviation criteria will be established and patients with major protocol deviations will be identified and documented before the database lock. Major protocol deviations will be presented for the Safety Analysis Set in a listing.

6.3.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including following variables will be summarized using descriptive statistics:

- Race
- Age (years) and age group (years) as < 65, ≥ 65
- Ethnicity
- Eastern Cooperative Oncology Group (ECOG) performance status at screening
- Time form initial diagnosis to study entry (Year)
- Metastases (Liver or lung)
- Baseline PSA
- Baseline hemoglobin
- Baseline LDH
- Baseline ALP

6.3.4 Prior Anti-Cancer Systemic Therapies

The number of prior line of anti-cancer therapies and number of prior regimens will be summarized by cohort and overall for the Safety Analysis Set. The therapies with the same sequence/regimen number are counted as one prior therapy.

6.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number and percentage of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term for the Safety Analysis Set by cohort and overall. Prior medications are defined as medications that started and ended before the first dose date. Concomitant medications are defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after

the patient's last dose or initiation of a new anti-cancer therapy. A listing of prior and concomitant medications will be provided.

6.3.6 Medical History

Medical History will be coded using MedDRA (version 20.0 or higher). The number and percentage of patients reporting a history of any medical condition, as recorded on the electronic case report form (eCRF), will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Analysis Set by cohort and overall. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

Table 2 summarizes the primary and secondary efficacy endpoints and corresponding analysis populations. If applicable, the specific cohort(s) or evaluable population being analyzed for each efficacy analysis will be specified.

Table 2 Primary and Secondary Efficacy Endpoint Analysis Populations

	Efficacy Endpoint	Analysis Population
Primary	ORR by IRC	Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1)
	PSA Response	Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2)
Secondary	DOR by IRC	Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1), those w/objective response per IRC
	ORR by INV	Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1)
	Time to Objective Response by INV	Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1), those w/confirmed objective response per INV
	Clinical Benefit Rate by INV	Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1)
	Time to PSA Response	Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2), those w/confirmed PSA response
	Duration of PSA Response	Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2), those w/confirmed PSA response
	Time to PSA Progression	Safety Analysis Set (Cohorts 1 and 2)
	Time to SSE	Safety Analysis Set (Cohorts 1 and 2)
	rPFS by IRC	Safety Analysis Set (Cohorts 1 and 2)
	OS	Safety Analysis Set (Cohorts 1 and 2)

Abbreviations: DOR = duration of response; INV = investigator; IRC = independent review committee; ORR = objective response rate; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SSE = symptomatic skeletal event.

6.4.1 Primary Efficacy Endpoints

Objective Response Rate (ORR) by IRC

ORR is defined as the proportion of patients with a best objective response of CR or PR confirmed at a subsequent timepoint ≥ 4 weeks later. For this primary efficacy endpoint, the tumor assessments will be performed by the IRC and will be summarized for the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1).

ORR (number and proportion of patients) will be presented along with its Clopper-Pearson 2-sided 95% confidence interval. The number and proportion of patients who achieve an unconfirmed best objective response of CR or PR will also be summarized.

ORR will be tested against a historical control ORR, and the null and alternative hypotheses are as follows:

H_0: ORR = 15%

H_a: ORR > 15%

A binomial exact test will be performed for the above hypotheses at a one-sided 0.025 significance level. If the result for ORR is statistically significant, ie, one-sided p-value < 0.025, then the primary efficacy endpoint of PSA response rate will be tested for statistical significance.

If the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1) is not equivalent to the Safety Analysis Set for Cohort 1, a sensitivity analysis of ORR will be conducted on the Safety Analysis Set for Cohort 1. The sensitivity analysis will be carried out in the Safety Analysis Set. Patients without postbaseline tumor assessment will be considered as non-responders in the Safety Analysis Set and will be classified as "not assessed."

Waterfall plots will be provided for the maximum tumor shrinkage from baseline based on the sum of diameters of all target lesions.

Subgroup analyses for ORR will be performed as described in Section 6.4.3.

PSA Response Rate

PSA response rate is defined as the proportion of patients with a PSA decline ≥ 50% from baseline confirmed by a second PSA value ≥ 3 weeks later. For this primary efficacy endpoint, the PSA assessments will be summarized for the Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2).

PSA response rate (number and proportion of patients) will be presented along with its Clopper-Pearson 2-sided 95% confidence interval. The number and proportion of patients who achieve an unconfirmed PSA decline ≥ 50% from baseline will also be summarized.

If the primary efficacy endpoint of ORR is statistically significant, PSA response rate will be tested against a historical control PSA response rate, and the null and alternative hypotheses are as follows:

H_0: PSA response rate = 30%

H_a: PSA response rate > 30%

A binomial exact test will be performed for the above hypotheses at a one-sided 0.025 significance level. If the result for PSA response rate is statistically significant, ie, one-sided p-value < 0.025, then PSA response rate will be considered statistically significant. Note that if the primary efficacy endpoint of ORR is not statistically significant, then no claims of statistical significance can be made for the primary efficacy endpoint of PSA response rate.

If the Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2) is not equivalent to the Safety Analysis Set for Cohorts 1 and 2, a sensitivity analysis of PSA response rate will be conducted on the Safety Analysis Set for Cohorts 1 and 2. The sensitivity analysis will be carried out in the Safety Analysis Set. Patients without postbaseline tumor assessment will be considered as non-responders in the Safety Analysis Set and will be classified as "not assessed."

Subgroup analyses for PSA response rate will be performed as described in Section 6.4.3.

6.4.2 Secondary Efficacy Endpoints

Duration of Response (DOR) by IRC

DOR is defined as the time from the date of the earliest documented CR or PR (that is subsequently confirmed) to radiographic disease progression or death due to any cause, whichever occurs first. The censoring rules for DOR will be similar to those for rPFS described in Appendix 10.2 except that the situation of "No baseline tumor assessments" will not apply to DOR. For this secondary efficacy endpoint, the tumor assessments will be performed by the IRC and will be summarized for patients in the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1) who have achieved a confirmed objective response.

DOR will be estimated using the Kaplan-Meier method, and the median DOR will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence intervals using Greenwood's formula.

ORR by Investigator (INV)

ORR is defined as for the primary efficacy endpoint. For this secondary efficacy endpoint, the tumor assessments will be performed by the investigator and will be summarized for the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1).

ORR (number and proportion of patients) will be presented along with its Clopper-Pearson 2-sided 95% confidence interval. The number and proportion of patients who achieve an unconfirmed best objective response of CR or PR will also be summarized.

Time to Objective Response by INV

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. For this secondary efficacy endpoint, the tumor assessments will be performed by the investigator and will be summarized for patients in the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1) who have achieved a confirmed objective response.

Time to objective response will be presented using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum).

Clinical Benefit Rate by INV

Clinical benefit rate is defined as the proportion of patients with a documented confirmed CR, PR or SD. For this secondary efficacy endpoint, the tumor assessments will be performed by the investigator and will be summarized for the Efficacy-Evaluable Analysis Set (ORR Assessment in Cohort 1).

The clinical benefit rate (number and proportion of patients) will be presented along with its Clopper-Pearson 2-sided 95% confidence interval.

Time to PSA Response

Time to PSA response is defined as the time from the date of the first dose of study drug to the first PSA decline ≥ 50% that is subsequently confirmed. For this secondary efficacy endpoint, the PSA assessments will be summarized for patients in the Efficacy-Evaluable Analysis Set (PSA Response Rate Assessment in Cohorts 1 and 2) who have achieved a confirmed PSA response.

Time to PSA response will be presented using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum).

Duration of PSA Response

Duration of PSA response is defined as the time from the date of the earliest documented PSA response (that is subsequently confirmed) to PSA progression or death due to any cause, whichever occurs first. PSA progression is defined as 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. The nadir is defined as the lowest value at or after baseline. For patients who have not died or had a PSA progression event as of the data cutoff date, duration of PSA response will be censored at the date of the last PSA assessment. The PSA assessments will be summarized for patients in the Efficacy-Evaluable Analysis Set

(PSA Response Rate Assessment in Cohorts 1 and 2) who have achieved a confirmed PSA response.

Duration of PSA response will be estimated using the Kaplan-Meier method, and the median duration of PSA response will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method. The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence intervals using Greenwood's formula.

Time to PSA Progression

Time to PSA progression is defined as the time from the date of the first dose of study drug to the date of 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. For patients who have not had a PSA progression event as of the data cutoff date, time to PSA progression will be censored at the date of the last PSA assessment. For this secondary efficacy endpoint, the PSA assessments will be summarized for the Safety Analysis Set (Cohorts 1 and 2).

Time to PSA progression will be estimated using the Kaplan-Meier method, and the median time to PSA progression will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method. The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence intervals using Greenwood's formula.

Time to Symptomatic Skeletal Event (SSE)

Time to SSE is defined as the time from the date of the first dose of study drug to the date of the first symptomatic fracture, radiation or surgery to bone or spinal cord compression. For patients who have not had an SSE as of the data cutoff date, time to SSE will be censored at the date of the last visit. This secondary efficacy endpoint will be summarized for the Safety Analysis Set (Cohorts 1 and 2).

Time to SSE will be estimated using the Kaplan-Meier method, and the median time to SSE will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method. The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence intervals using Greenwood's formula.

Radiographic Progression-Free Survival (rPFS) by IRC

rPFS is defined as the time from the date of the first dose of study drug to radiographic disease progression or death due to any cause, whichever occurs first. Censoring rules for rPFS will be described in Appendix 10.2. For this secondary efficacy endpoint, the tumor assessments will be performed by the IRC and will be summarized for the Safety Analysis Set (Cohorts 1 and 2).

rPFS will be estimated using the Kaplan-Meier method, and the median rPFS will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method. The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence

intervals using Greenwood's formula. The median follow-up will be estimated using the reverse Kaplan-Meier.

Overall Survival (OS)

OS is defined as the time from the date of the first dose of study drug to death due to any cause. Patients who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of data cutoff or the last date the patient was known to be alive. This secondary efficacy endpoint will be summarized for the Safety Analysis Set (Cohorts 1 and 2).

OS will be estimated using the Kaplan-Meier method, and the median OS will be presented along with its 2-sided 95% confidence interval using the Brookmeyer and Crowley method. The event-free rate at select timepoints will be calculated along with 2-sided 95% confidence intervals using Greenwood's formula. The median follow-up will be estimated using the reverse Kaplan-Meier.

6.4.3 Subgroup Analyses

The primary efficacy endpoints of ORR and PSA response rate will be summarized within their respective analysis populations for the following subgroups:

- Age group (< 65 years vs ≥ 65 years)
- Race (White vs other)
- Geographic Region (North America vs rest of world)
- ECOG performance status (0 vs 1)
- BRCA 1/2-mutant status (mutated vs unmutated)
- Number of prior lines of therapy (0-2 vs 3+)

6.4.4 Exploratory Efficacy Endpoints

[redacted]

Table 3 Exploratory Efficacy Endpoint Analysis Populations

[redacted]

[redacted]

[redacted]

6.5 SAFETY ANALYSES

All safety analyses will be performed by cohort and overall for the Safety Analysis Set. The incidence of treatment-emergent adverse events (TEAEs) will be summarized. Laboratory test results and vital signs will be provided in listings.

6.5.1 Extent of Exposure

The number (and percentage) of patients requiring dose reductions, dose missed and dose on hold will be summarized. One cycle is defined as 28 days of treatment. The duration of treatment (days) will be summarized with descriptive statistics.

Actual dose intensity per patient (in mg/day) and relative dose intensity (total dose received / total dose planned) per patient will be summarized. Actual dose intensity is calculated as the total dose (mg) taken by a patient divided by overall duration of exposure (= Date of last non-zero dose – Date of first dose + 1) for individual patient. Relative dose intensity is calculated as the total dose (mg) taken by a patient divided by the total dose planned for the patient by study design.

Patient data listings will be provided for all dosing records, including dose reduction, dose missed and treatment discontinuation.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher.

A treatment emergent adverse event (TEAE) is defined as an AE that had an onset (including worsening from pretreatment) date on or after the first dose of study treatment through 30 days after the last dose of study treatment or initiation of new anti-cancer therapy, whichever occurs first. Only TEAEs will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

An overview table, including the number and percentage of patients with TEAEs, serious TEAEs, grade 3 or higher TEAEs, treatment-related TEAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number and percentage of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. The number and percentage of patients will be summarized by SOC and/or PT for the following:

- TEAEs

- Treatment Related Grade 3 or higher TEAEs
- Serious TEAEs
- TEAEs that led to treatment discontinuation
- TEAEs that led to dose modification

TEAEs will also be summarized by PT in descending order. A listing of all AEs and AEs that led to treatment discontinuation will be provided.

All deaths and causes of death will be provided in a listing, including those occurring during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

6.5.3 Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 4.

Laboratory parameters that are graded in NCI CTCAE v.4.03 will be summarized by grade, and shift tables (baseline grade to maximum post-baseline grade) will be provided. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. The number and percentage of patients with abnormal liver laboratory values will be summarized.

Patient data listings of selected hematology, serum chemistry parameters and urinalysis will be provided.

Table 4 Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	Hematology
Alkaline phosphatase (ALP)	Hemoglobin
Alanine aminotransferase (ALT)	Platelet counts
Aspartate aminotransferase (AST)	White blood cell (WBC) count
Albumin	Neutrophil (Absolute)
Total bilirubin	Lymphocyte (Absolute)
Blood Urea Nitrogen	
Creatinine	
Chloride	
Phosphate	
Glucose	
Lactate dehydrogenase (LDH)	
Total Protein	
Potassium	
Sodium	

6.5.4 ECOG Performance Status

A shift table from baseline to worst post-baseline ECOG performance score will be summarized by cohort and overall for the Safety Analysis Set. ECOG scores will be summarized by visit.

6.6 PHARMACOKINETIC ANALYSIS

BGB-290 concentrations after single-dose and at steady-state will be summarized by the sampling timepoint. Descriptive statistics will include means, medians, standard deviation, arithmetic coefficient of variation (ACV) and geometric coefficient of variation (GCV) as appropriate. ACV is calculated in original scale with the equation $100 \times \mathrm{SD}/\mathrm{AM}$ and GCV is calculated in natural log-scale with the equation: $\sqrt{(e\text{^}(\sigma\text{^}2\ ) - 1) \times 100}$, where σ^2 is the observed variance on the natural log scale. If a patient undergoes dose modification (e.g. dose reduction or study drug discontinuation) before steady-state PK collection, then that patient's steady-state concentrations will be excluded from summary statistics.
Population PK analysis may be carried out to include plasma concentrations from this study. Additional PK parameters such as CL/F of the drug from plasma and $AUC_{0\text{-}12}$ 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.

6.7 BIOMARKER ANALYSIS

Baseline blood samples for ctDNA analyses will be subjected to next generation sequencing. In addition, available archival tissue samples will be subjected to Myriad MyChoice testing for homologous recombination deficiency determination.

7 INTERIM ANALYSIS

A non-binding interim futility analysis will be performed among the first 20 patients enrolled in Cohorts 1 and 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.

8 CHANGES IN THE PLANNED ANALYSIS

Due to upcoming changes in standard of care, changes in program strategy, slow enrolment and apparent lack of responses, the trial was terminated after enrolling 13 patients in cohort 1B and cohort 2B. The final clinical study report will not include all the planned analyses per protocol including the interim analysis because the milestone of enrolling 20 patients was not reached.
For the final clinical study report, tables of patient disposition and reasons for discontinuation, demographics and baseline characteristics and prior anti-cancer therapies will be provided. No efficacy related tables or analysis will be conducted. Tumor assessment result by investigator (target lesions by time point and bone lesions) will be listed but result by IRC will not be

included in the final clinical study report, because of the small number of patients enrolled and the fact that the majority of the patients did not had postbaseline tumor assessments. HRQoL data results will be listed. Data from PSA assessments will be provided in listings and discussed in the clinical study report. Exposure data, safety analyses and PK analyses will be conducted as planned. ECOG performance shift table will not be conducted. The biomarker data will be provided as listings.

9 REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982 Mar;38(1):29-41.

Cleeland CS. The Brief Pain Inventory: User Guide. 2009

Clopper, C. and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika 1934;26: 404-413.

Collett D. Modelling survival data in medical research. New York: Chapman & Hall; 1994.
Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, May 28, 2009.

EQ-5D-5L User Guide. EuroQol Research Foundation 2015. www.euroqol.org

Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research. FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2018.

Greenwood M. “The natural duration of cancer”. Reports on Public Health and Medical Subjects (London: Her Majesty’s Stationery Office). 1926; 33:1-26.

Gordon John Sampson Rustin, etc. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21: 419-423.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Washington, DC: United States Food and Drug Administration; 2007.
Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.

10 APPENDICES

10.1 HANDLING MISSING DATE INFORMATION

In general, missing or partial dates will not be imputed at data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

10.1.1 Prior/Concomitant Medications, Disease and Medical History, Prior Therapy (Drug, Surgery/Procedure, Radiotherapy)

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute missing or partial dates for medications /therapy/procedure:

	Missing	Impute	Exception
Start Date	Day	01	N/A
	Day/Month	January 01	N/A
	Day/Month/Year or Year only	Do not impute	N/A
End Date	Day	Last day of the month	N/A
	Day/Month	December 31	N/A
	Day/Month/Year or Year only	Do not impute	N/A

If the imputed start date becomes after end date, then update start date same as end date. And if the imputed start date or end date becomes after death date, then set to death date.

For disease history, medical history and prior therapy (ie Chemotherapy, hormonal therapy, biologic therapy, radionuclide therapy, immunotherapy, investigational agent, Chinese anticancer medicine, or herbal remedies), including relapse date, therapy date (start/end date), or surgery date, if the imputed start date or end date becomes after first dose date, then set to first dose date - 15. For radiotherapy, if the imputed start date or end date becomes after first dose date, then set to first dose date - 22.

10.1.2 Initial Diagnosis and Most Recent Progression

For initial diagnosis date and most recent progression date, which has no duration and only start date is available, impute the date using the following rule:

	Missing	Impute	Exception
Initial Diagnosis Date/ Most Recent Progression Date	Day	01	N/A
	Day/Month	January 01	N/A
	Day/Month/Year or Year only	Do not impute	N/A

If the imputed initial diagnosis date or most recent progression date is on or after the treatment start date, then set to treatment start date - 1.

10.1.3 Adverse Events

The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute missing or partial dates for adverse events:

	Missing	Impute	Exception
Start Date	Day	01	If Month and Year = Month and Year of treatment start date, the set to treatment start date
	Day / Month	January 01	If Year = Year of treatment start date, then set to treatment start date
	Day / Month / Year or Year only	Do not impute	If AE End Date > treatment start date, then set to treatment start date
End Date	Day	Last day of the month	N/A
	Day / Month	December 31	N/A

Day / Month / Year or Year only	Do not impute	N/A

If the imputed AE start date becomes after AE end date, then update AE start date same as AE end date. And if the imputed start date or end date becomes after death date, then set to death date.

The following rule will be applied to impute missing toxicity grade of AE:

1. The highest grade will be used from patient's AEs with the same preferred term.
2. If patient has no AEs with the same preferred terms, the highest grade of the AEs with the same SOC will be used.
3. If patient has no same SOC, the highest grade of all AEs from that patient will be used.
4. If it is the single AE reported for that patient, no imputation for the missing grade will be done.

10.1.4 Deaths

In case complete death dates are not recorded, impute as follows:

- If both month and day are missing, then the imputed month and day will be 01Jan or the last date of the last date of patient known to be alive + 1, whichever is later.
- If only day is missing, the death will be assumed to be on the first day of the month or the last date of patient known to be alive +1, whichever is later.

10.1.5 New Anticancer therapy

If the start day of a subsequent anticancer therapy is incomplete or missing, impute as follows:

- if both month and day are missing,
  1) impute the date as 31Dec, if the year is earlier than the year of the first PD date + 1 or the treatment end date + 1, whichever is later
  2) impute the date as 01Jan, if the year is later than the year of the first PD date or the treatment end date + 1, whichever is later
  3) impute the date as the first PD date + 1 or the treatment end date + 1, whichever is later, if the year is the same year of first PD date + 1 or the treatment end date + 1, whichever is later
- if only day is missing,
  1) impute the date as the first day of the month if year and month are available and partial new anticancer therapy date still could indicate it is at least one month later than the first PD date +1 or the treatment end date +1, whichever is later.

2) impute the date as the last day of the month if year and month are available and partial new anticancer therapy date still could indicate it is at least one month earlier than the first PD date +1 or the treatment end date +1, whichever is later.

3) Impute the date as the first PD date +1 or the treatment end date +1, whichever is later, if the year and month are the same year and month of first PD date +1 or the treatment end date +1, whichever is later.

10.2 CENSORING RULES

Table 5 shows the primary censoring rules for the derivation of rPFS.

Table 5 Censoring Rules for Analysis of rPFS

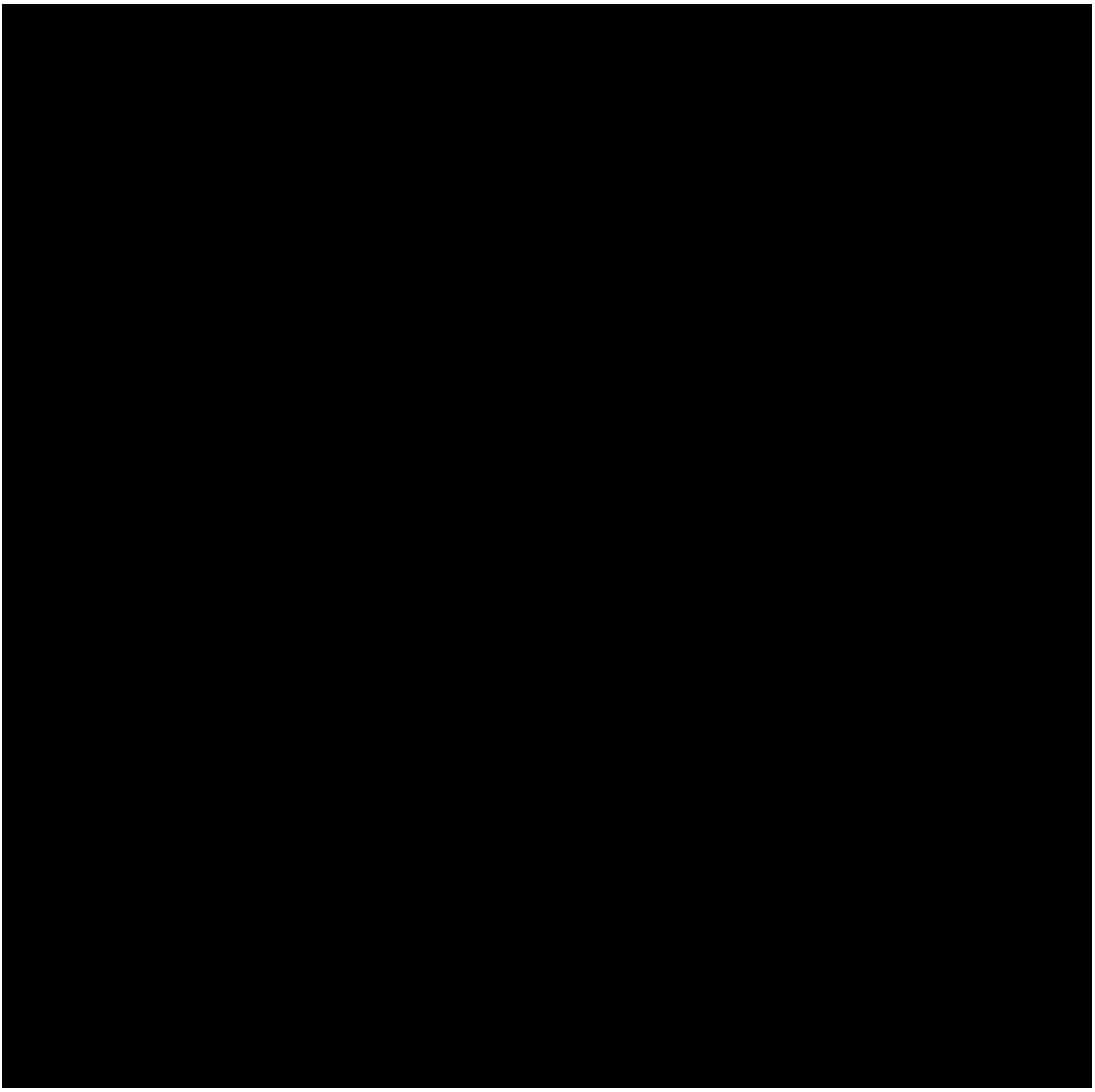
No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments or no post-baseline tumor assessment	Reference start date	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cutoff or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cutoff or withdrawal from study	Censored
4	Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
5	New anticancer treatment started	Date of last radiological assessment of measured lesions prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Progressed
7	Death between adequate assessment visits*	Date of death	Progressed
8	Death or PD after two or more consecutive missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored
9	A patient meets the criteria for more than 1 censoring rule	Date of the earliest censoring date among all events	Censored

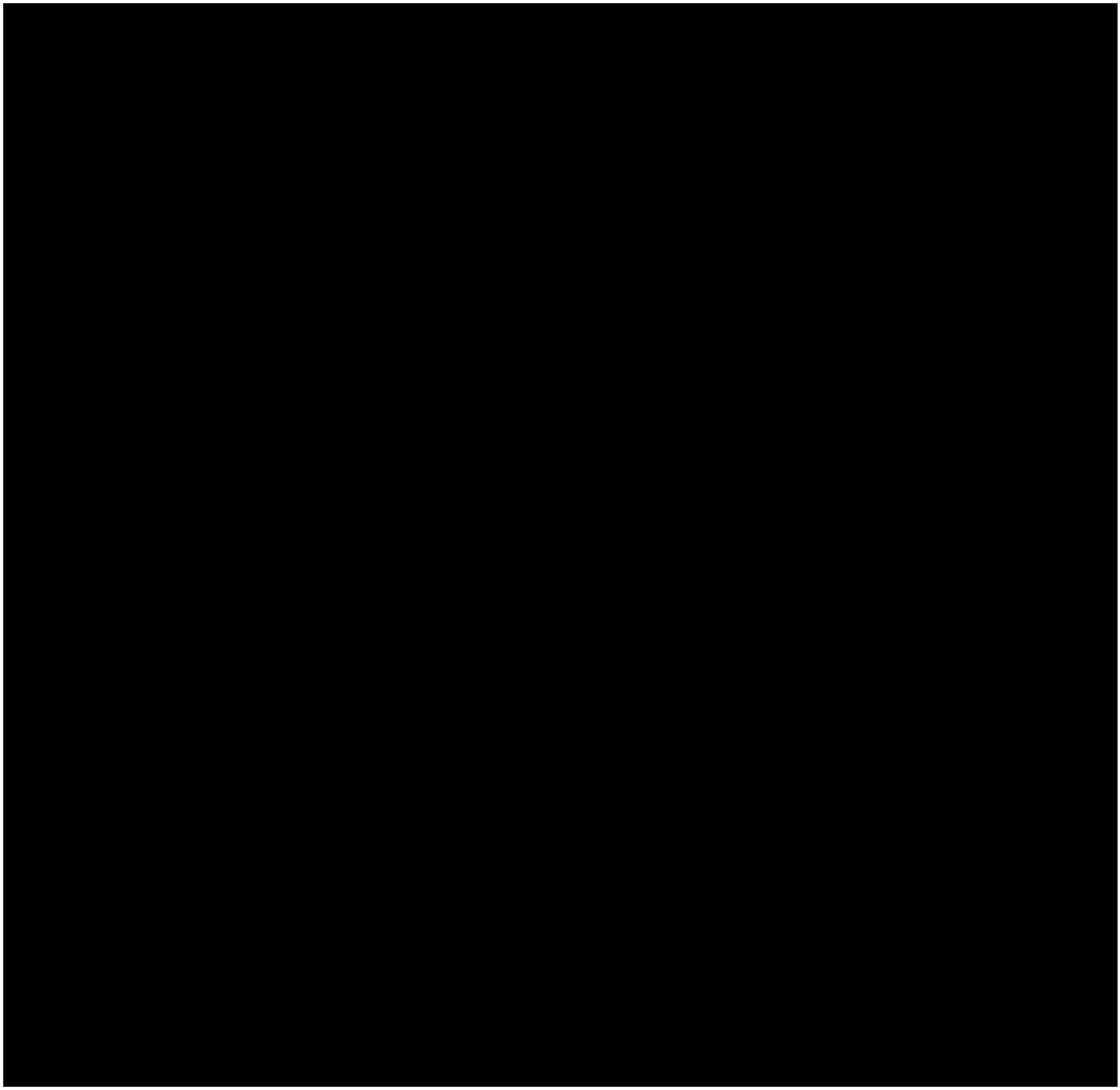
Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease.

*Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators or by IRC.

**More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 2 scheduled visits.

10.3 PROs: INSTRUMENTS AND SCORING METHODS





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