STATISTICAL ANALYSIS PLAN

A PHASE 1 TRIAL OF THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY CLINICAL ACTIVITY OF RP-3467 ALONE AND IN COMBINATION WITH OLAPARIB IN PARTICIPANTS WITH ADVANCED SOLID TUMORS (POLAR TRIAL)

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[redacted]

Version History

Version and Date	Description
Version 1.0, 29SEP2025	Original Version
Version 1.1, 19NOV2025	Update to Table 8 in Appendix Section 12.1.1 to require documented BOR of SD at least once 6 weeks from the first dose of trial intervention, instead of 8 weeks as stated in previous version, to better align with study protocol and instructions outlined in Section 7.1.1 of this document.

CONTENTS

[redacted]

ABBREVIATIONS AND ACRONYMS

Abbreviation or Specialist Term	Explanation
ADI	Actual Dose Intensity
AE	Adverse event
ANC	Absolute neutrophil count
ATC	Anatomical Therapeutic Class
AUC	Area under
BID	Twice-daily
BOIN	Bayesian optimal interval
BOR	Best overall response
CA-125	Cancer antigen 125
CBR	Clinical benefit rate
CI	Confidence Interval
CR	Complete response
CRR	Composite response rate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
ctDNA	Circulating tumor DNA
DOR	Duration of response
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End-of-treatment
eCRF	Electronic case report form
GCIG	Gynecologic Cancer Intergroup criteria
HR	Homologous recombination
ICF	Informed consent Form
IHC	Immunohistochemistry
LLOQ	Lower limit of quantitation
MTD	Maximum Tolerated Dose

Abbreviation or Specialist Term	Explanation
MAD	Maximum Administered Dose
MMEJ/TMEJ	Microhomology or theta mediated end joining
MR	Minor Response
NCA	Non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
ORR	Objective response rate
PCWG3	Prostate Cancer Working Group criteria
PD	Progressive disease
PDI	Planned Dose Intensity
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PSA	Prostate specific antigen
PT	Preferred Term
QD	Daily
RBC	Red blood cell
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable disease
SOC	System organ classification
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse events
TL	Target lesion
T_{max}	Time to maximum observed plasma concentration
$t_{1/2}$	Elimination half-life
ULN	Upper limit of normal
VAF	Variant allele frequency

1. INTRODUCTION

This document describes the statistical methods to be implemented in the statistical analysis of data collected under clinical study Protocol RP-3467-01, titled: "Phase 1 Trial of the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Clinical Activity of RP-3467 Alone and in Combination with Olaparib in Participants with Advanced Solid Tumors (POLAR Trial)". This Statistical Analysis Plan (SAP) contains definitions of analysis populations, derived variables, statistical methods for the analyses of baseline, [redacted] and safety data and the data listings and summary tables which will be produced. Details will be described to ensure the results are complete and appropriate to allow valid conclusion regarding the study objectives.

The analysis details for pharmacokinetic, pharmacodynamics, and biomarker analyses are not described within this SAP. A separate analysis plan may be implemented for those analyses.

This document has been prepared based on Protocol Version 2.0, dated July 17, 2024.

2. STUDY OVERVIEW

This is a multicenter, open-label Phase 1 trial to investigate the safety, [redacted] pharmacodynamic, and preliminary efficacy of the Polθ inhibitor RP-3467 alone or in combination with the poly-ADP ribose polymerase (PARP) inhibitor (PARPi) olaparib in participants with molecularly selected advanced solid tumors. The trial is estimated to enroll approximately 52 evaluable participants with any of the following types of tumors:

- Locally advanced or metastatic epithelial ovarian cancer (including fallopian tube or primary peritoneal)
- Metastatic breast cancer
- Metastatic castration-resistance prostate cancer (mCRPC)
- Pancreatic adenocarcinoma

In addition, these participants harbor any one of the following in their biomarker profile:

- Deleterious alteration of BRCA1/2, PALB2, RAD51B/C/D
- Homologous recombination deficiency (HRD+)

Preclinical studies demonstrate that Polθ inhibition sensitizes HR deficient cells to PARPi which is consistent with reliance on microhomology or theta mediated end joining (MMEJ) by homologous recombination (HR) deficient tumors.

2.1 Study Design

The trial will follow a Bayesian Optimal Interval (BOIN) design to guide escalation and de-escalation decision for both monotherapy (Arm 1) and combination therapy (Arm 2) respectively, to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD), and to identify a dose of RP-3467 alone and in combination with olaparib that is tolerable.

[redacted]

[redacted]

The starting dose (Dose Level 1) for Arm 1 is 160 mg once daily (QD). The staring dose for RP-3467 in Arm 2 will be at least one level lower than the highest monotherapy dose level considered safe by the SRC. The starting dose of olarparib will be 200 mg twice a day (BID). Once safety of olaparib used in combination with RP-3467 is confirmed, the dose of olaparib may be increased to the USPI recommended dose of 300 mg BID for subsequent cohorts.

Escalation in Arm 1 (monotherapy) will proceed with up to 100% increases in RP-3467 after evaluation of tolerability by the SRC until Dose Level N. Dose Level N is defined as the dose level at which any of the following safety signals occur:

- Any ≥ Grade 3 hematological toxicity
- >50% decrease in platelets or neutrophils from the first dose
- >2 g/dL decrease in hemoglobin from the first dose
- Any ≥ Grade 2 drug-related non-hematological toxicity lasting >5 days or requiring clinical intervention, except Grade 2 fatigue, nausea, vomiting, diarrhea, or constipation
- Any adverse event (AE) of any grade limiting tolerability as assessed by the SRC

After dose level n is reached, subsequent dose levels of RP-3467 may be increased by 75% or a modified Fibonacci sequence per SRC discretion based on the safety profile observed.

Dose escalations in Arm 2 (RP-3467 with olaparib) will be guided by dose levels in Arm 1(RP-3467 monotherapy). The same criteria guiding dose escalations in Arm 1 will be used to determine escalations of RP-3467 in Arm 2 if the events occur during the DLT evaluation period.

Once a dose level is reached that results in maximally efficacious RP-3467 exposure in Arm 2: RP-3467 with olaparib, this dose level may be expanded to at least 6 participants to better assess safety/tolerability [redacted].

Table 1: Dose Levels of RP-3467

Dose Level	Arm 1	Arm 2	Escalation Plan
	RP-3467 Daily (mg)[a] or % of pervious dose	RP-3467 Daily (mg)[a]	Olaparib (mg, BID)
-1a	NA	80	200
-1b[b]			300[b]
1	160	RP-3467 dose not higher than corresponding Arm 1 DL	300
2	Up to 100% increase until level N		300

The BOIN design will guide dose level escalations/de-escalations using the following rules for both Arm 1 (RP-3467 monotherapy) and Arm 2 (RP-3467 with olaparib), targeting a 25% DLT rate:

- If the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level;
- If it is > 0.298, de-escalate the dose to the next lower dose level;
- Otherwise, stay at the current dose.

A 3+3 decision criteria will be applied if the number of participants treated at the current dose is 3. Meaning, if 0/3 participants experience a DLT at the current dose, then the dose will be escalated. If 1/3 participants experience a DLT, then the dose will stay at the current level, and the dose will de-escalate if ≥2/3 participants experience a DLT. The rules for dose escalation/de-escalation can be summarized in the following table.

Table 2: Dose Escalation/De-Escalation Rules for the BOIN Design

	Number of DLT Evaluable Participants at Current Dose Level								
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
↑ if number of DLT ≤	0	0	0	0	0	1	1	1	1
↓ if number of DLT ≥	1	1	2*	2	2	2	3	3	3
Elim if number of DLT ≥	NA	NA	3	3	3	4	4	4	5

BOIN = Bayesian optimal interval; ↑ = increase, ↓ = decrease, DLT = dose-limiting toxicity, Elim=eliminate, NA = not applicable, dose cannot be eliminated until at least 3 participants have been treated and are DLT evaluable
Note: # of DLT is the number of participants with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of participants.
* Based on the 3+3 design run-in.

If a determination is made to eliminate based on the criteria in Table 2, then the current dose and all higher concentrations are eliminated, and the dose is automatically de-escalated one level. If none of the actions (escalation, de-escalation, elimination) are triggered, participants will continue to be enrolled at the current dose. Dose escalation/de-escalation will continue until the maximum total sample size is reached (n~36), 9 participants are enrolled at the current dosing level and the decision is made to maintain the current dose according to the rules outlined in Table 2, or the SRC decides to stop.

Monotherapy dose escalation may be stopped before establishment of an MTD if

- [redacted]
- MTD is exceeded in the combination dose-escalation arm

Intrapatient dose escalations of RP-3467 or olaparib (from 200 mg BID to 300 BID) may be allowed at the discretion of the investigator and with Sponsor approval.

[redacted]

Once an MTD [redacted] has been established for Arm 2: RP-3467 with olaparib, backfill cohorts up to 8 evaluable participants may be enrolled. The objectives of the backfill cohorts are to aid in the assessment of antitumor activity, [redacted] and further optimize dose.

After the trial is completed, results from all participants including the backfill cohorts will be included to assess safety [redacted]. The MTD can be determined based on the isotonic estimate of the toxicity that is closest to the target toxicity. [redacted]

2.2 Study Procedure and Assessment

The trial will consist of a Pre-Screening Period (within 6 months from time enrollment, to confirm molecular eligibility), Screening Period (28 days, to determine eligibility), a 2-day PK run-in, Treatment Period (21-Day cycles), an End of Treatment (EOT) Visit (occurring after the last dose and within 7 days after the discontinuation of trial treatment date), a Safety Follow-up Visit (occurring within 30 days ± 14 days after the last dose of trial treatment), and a Long-Term Follow Up period (for up to 24 months after the discontinuation of treatment date). The end of Trial is defined as the date of the last visit (including all follow-up visit) of the last participant in the trial.

2.3 Sample Size

The approximate total number of participants for this trial is 52 evaluable patients. This will include approximately 36 participants in dose escalation (both monotherapy and combination therapy) and 16 participants in backfill cohorts. Additional participants may be added to account for non-DLT evaluable participants in the dose escalation cohorts and participants in backfill cohorts with less than 1 full cycle of treatment.

The sample size for dose escalation is not driven by statistics but determined based on number of dose escalations that will potentially be assessed. It is estimated that approximately 12 participants (up to 4 dose levels) are needed for the monotherapy dose escalation (Arm 1) due to the minimum toxicity expected, and approximately 24 participants for the combination escalation phase (Arm 2) with estimated up to 5 potential dose levels for the combination.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objectives

- To assess the safety and tolerability of RP-3467 alone and in combination in participants with eligible, advanced solid tumors and to define the MTD or MAD for RP-3467 monotherapy

[redacted]

3.2 Endpoints

3.2.1 Primary Endpoints

- DLTs, incidence and severity of TEAEs

[redacted]

[redacted]

4. ANALYSIS POPULATIONS

The following analysis populations will be used for statistical analysis.

4.1 DLT Evaluable Population

The DLT Evaluable Population will consist of participants who have met the minimum safety evaluation requirements of the trial and /or who experience a DLT at any time during the DLT evaluation period (from the start of treatment through the end of Cycle 1). Minimum safety requirements will be met if, during Cycle 1 of treatment, the participant receives at least 75% of their planned total dose of RP-3467 and olaparib (if applicable), completes required safety evaluations and is observed through the end of Cycle 1 since the first dose of trial intervention. Administration of growth factors or transfusions during the DLT evaluation period for hematologic events not meeting DLT criteria will render a participant not DLT evaluable. DLT evaluability will be recorded in the appropriate CRF and used to determine the DLT evaluable population. The DLT evaluable population will be used to determine DLT rate of the dose levels.

4.2 Safety Population

The Safety Population, used for the assessment of overall safety and tolerability, will consist of all participants who receive at least 1 dose of RP-3467. The analysis set will be used for individual listings, disposition summary table and all safety analyses, unless otherwise specified.

[redacted]

5. DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

All analyses will be performed using SAS® Version 9.4 or higher.

Unless specified otherwise, the analyses of data collected will be descriptive and summaries will be presented separately for each dose level, dose schedule (if applicable) and in total for the specified analysis population. Statistical analysis will be purely descriptive and no formal hypothesis testing or comparative analysis between dose level will be performed. Confidence intervals (CIs) will be constructed at two-side 95% level where appropriate.

Frequency distributions for categorical variables will be provided as the number of subjects in the category and the percentages of the total number of subjects in the given population as noted. Percentages will be reported to one decimal place.

The descriptive statistics for continuous variables will be the number of subjects, mean, standard deviation, median, lower and upper quartile, minimum and maximum. Mean, median will be reported to 1 decimal place, while the standard deviation will be reported to 2 decimal places. Minimum and maximum will be reported the same as the original data.

Summary tables may be replaced with listings when appropriate. For instance, an AE Frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few subjects.

All tables will be summarized by treatment regimen (Arm 1 and Arm 2 respectively), dose level, and dose schedule, and include an overall column for Arm 1 and Arm 2 respectively unless otherwise specified.

All listings will be sorted by arm, dose level, and dose schedule if applicable, subject ID and, if applicable, by visit date unless otherwise specified in the text.

5.1 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to the first administration of RP-3467 or olaparib, whichever occurs first.

- Change from baseline is calculated as (Value at a visit – Baseline Value)
- Percent change from baseline is calculated as (Value at a visit – Baseline value)/Baseline value * 100

5.2 Definition of Treatment Emergent Period

Unless otherwise stated, derivations of the worst post-treatment value will be assessed within the confines of the treatment emergent period, defined as the time from the start of study treatment, until 30 days after the last dose of RP-3467 or olaparib, the participant starts a subsequent anti-cancer therapy, or the participant is taking the monotherapy treatment and starts olaparib treatment, whichever occurs first.

5.3 Definition of Resue Period

For rescue arm patients who have been crossed over to the protocol-defined rescue treatment (combination therapy after treatment with monotherapy), the rescue period is defined as the time between the first dose of the co-therapy olaparib to study treatment discontinuation.

5.4 Definition of Study Days

Unless otherwise noted, study days of an evaluation are defined as the number of days relative to the first dose date which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc.

Study days are calculated as

- (Date of assessment – first dose date + 1) for assessments on/after first dose date.
- (Date of assessment – first dose date) for assessments before first dose date.

5.5 Analysis Visit Window

Data will be analyzed by scheduled visits, where appropriate. Data collected from an unscheduled visit will not be included in the by-visit summary tables but will be presented in the listings. However, data collected at Unscheduled Visit will also be considered for toxicity grading for laboratory assessments. [redacted]

5.6 Handling of Missing/Partial Dates for Adverse Events

If the start or end date for an AE is partially or completely missing, the date will first be queried for resolution if possible. If the year of the start date is missing or the start date is completely missing, the first dose date will be used. If the year of the end date is missing or the end date is completely missing, the event will be regarded as ongoing. Impute AE end date first if both AE start date and end date are partially missing.

If end date of an adverse event is partially missing, impute as follows:

- If the day of the month is missing, the onset day will be set to the last day of the month.
- If the onset day and month are both missing, the day and month will be assumed to be December 31.
- If the imputed end date > death date, then set to death date.

If start date of an adverse event is partially missing, impute as follows:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is on or after the same month and year as study treatment. In this case, the onset date will be assumed to be the first dose date of treatment or co-therapy, whichever comes first.
- If the onset day and month are both missing, the day and month will be assumed to be January 1 when the year is on or after the year of study treatment. If the year is prior to year of first dose, December 31st will be used. The event onset will be coded to the first dose date of treatment if year is the same as the year of first dose date to conservatively report the event as treatment-emergent.
- If the imputed AE start date is after the AE end date (maybe imputed), then update the AE start date with the AE end date as the final imputed AE start date.
- If the imputed start date > death date, then set to death date
- If the imputed end date is before imputed start date, the AE event will be treated as treatment emergent AE and report it as data issue.

Imputation of partial dates is used only to determine whether an event is treatment-emergent or the duration of the event. A flag will indicate if the start or end date was imputed respectively. Data listings will present the partial date as recorded in the eCRF.

5.7 Handling of Missing/Partial Dates for Non Anti-cancer Medications/Procedures/Therapy

When the start date or end date of a medication/therapy/procedure, that is not anti-cancer therapy, 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 partial dates for medications. The first dose date will be the date of the first dose of RP-3467 or olaparib, whichever occurs first.

If the start date of a medication/procedure/therapy is partially missing, impute as follows:

- Medication/procedure/therapy start dates with a missing day and non-missing month will be assumed to have occurred on the first day of the non-missing month if the month and year is after first dose date. If the month and year are prior to the first dose date, the last day of the month will be assigned to the missing day. If the month and year are the same as the first dose date, the first dose date will be used.
- Medication/procedure/therapy start dates with missing day and month will be assumed to have occurred on the first day of the non-missing year (i.e., 01 January) if the year is after the year of first dose date. If the year is prior to the year of first dose date, December 31 will be assigned to the missing fields. If the year is the same as the year of the first dose date, the first dose date will be used.
- If the imputed start date > death date, then set to death date and report it as data issue

If the end date of a medication/procedure/therapy is partially missing, impute as follows:

- Medications/procedure that are not ongoing and have a medication/procedure/therapy stop date with a missing day and non-missing month will be assumed to have stopped on the last day of the non-missing month.
- Medications/procedure that are not ongoing and have a medication/radiotherapy stop date with a missing month will be assumed to have stopped on the last day of the non-missing year (i.e., 31 December).
- If the imputed end date > death date, then set to death date and report it as data issue.
- If the imputed end date is before imputed start date, report it as data issue.

If the year of the start date or the year of the end date of a medication/procedure/therapy is missing, or the start date or end date is completely missing, do not impute.

5.8 Handling of Missing/Partial Dates during Screening Visit

The following rules apply to partially missing dates recorded during the screening visits (e.g. initial diagnosis), If date is completely missing, no imputation is needed:

- If the day of the month is missing, the first day of the month will be used if the year and the month are the same as the first dose of study days. Otherwise, the 15th will be used.

- If the day and month are both missing, the day and month will be assumed to be January 1 when the year is on the year of study treatment. If the year is prior or after the year of first dose date, the date of the first of July will be used, unless other data indicates the date is earlier.

5.9 Handling of Missing/Partial Dates for Prior Anticancer Therapy/Procedures

The following rules will be applied to impute partial dates such as prior systemic anticancer therapy or radiotherapy date (start/end date), or surgery date etc.

Impute end date first. If end date is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to the last day of the month
- For prior systemic therapy for cancer, if imputed end date > the first study drug date, then set to the first study drug date
- For prior radiotherapy, if imputed end date > the first study drug date, then set to the first study drug date - 1

If start date is partially missing, impute as follows:

- If both month and day are missing, then set to January 1st
- If only day is missing, then set to the first of the month
- If the imputed start date > end date, then set to the end date (the data should also be queried)

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

5.10 Handling of Missing/Partial dates for Post-study Anticancer Therapy/Radiotherapy

For records with completely missing start date, end of treatment date will be used as the start date of post-study therapy/radiotherapy. If the start date of post-study anticancer therapy/radiotherapy is partially missing, impute as follows:

- If the day of the month is missing, the start day will be set to the last day of the month unless it is on the same month and year as last dose of the study treatment. In this case, the start date will be assumed to be the last dose date + 1.
- If the day and month are both missing, the start date will be set to January 1st unless it is on the same year as the last dose date of the study treatment. In this case, the start date will be assumed to be the last dose date + 1.
- If only month is missing, year and day are present, set the missing month to the month of the last dosing date of the study drug unless the day is prior to the last dose day. In this case, impute the missing month as the month of last dose date + 1

No imputation is needed for post-study therapy/radiotherapy end date.

5.11 Handling of Partial Dates for Other Data

Other data with partial dates will be listed as collected. For calculations of time intervals listed [redacted] below, the dates will be imputed with the first day of the month (if the day is missing) or with January 1 (if both day and month are missing). If additional imputation is required, instructions will be provided in future amendments to this document.

5.12 Handling of Missing Data

Missing data will not be imputed, except for:

- Missing date parts, i.e., partial dates, discussed above.
- [redacted]
- Missing AE relationship to study drug [redacted].

6. STUDY SUBJECTS

6.1 Subject Enrollment

The number of subjects in each analysis set will be summarized for all patients. Analysis set flag for each subject will be listed together with the dose level and dose schedule for all patients.

6.2 Subjects Disposition

Subjects disposition will be summarized by dose level and dose schedule if applicable, and overall for the Safety Population including:

- Number of subjects treated in each safety [redacted] and DLT population.
- Number of subjects treated.
- Number of subjects who discontinued study treatment and primary reasons of discontinuation.
- Number of subjects who completed the study.
- Number of subjects who discontinued study and primary reasons of discontinuation by analysis population.

The primary reason for treatment discontinuation and study discontinuation will be summarized by categories in eCRF. Subjects' disposition will be listed for the Safety Population.

6.3 Protocol Deviations

Important protocol deviations are protocol deviations that may have significant impact on a patient's rights, safety, or well-being, or compromise the analysis and interpretation for the primary study endpoints. Protocol deviations will be identified and classified ongoing basis based on the protocol deviation plan and finalized prior to any database snapshot or database lock. Only important protocol deviations will be listed in a CSR for the Safety Population.

6.4 Demographics and Other Baseline Disease Characteristics

Demographic and baseline characteristics will be tabulated using descriptive statistics for the Safety Population. The following variables will be included:

- Age at Consent (years)
- Sex at birth
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (body mass index, kg/m^2), defined as weight (kg) / height $(m)^2$
- ECOG at Screening
- Genotype (BRCA1, BRCA2, PALB2, etc.)

- Tumor types (Prostrate adenocarcinoma, Pancreatic adenocarcinoma, breast carcinoma, Ovarian epithelial carcinoma)
- Histology Grade of disease at diagnosis (G1, G2, G3, G4, Gx, unknown, Other).
- Country of study site.

The below baseline disease characteristics may be further summarized (if applicable to majority of patients) or included in the subject listing:

- Time from initial diagnosis to first dose (Months) and time from diagnosis at Screening to first dose (Months), calculate as (Date of Informed Consent – Date of diagnosis + 1)/30.4375
- Molecular features (AR-V7, Other AR variant, Unknown, Other)
- Tumor primary location (Ovaries, Peritoneum, Fallopian tube, Multiple sites/Unknown)
- Histology Categories (Ductal carcinoma, Lobular carcinoma, High Grade serous, Low grade serous, endometrioid, clear cell, mucinous, Other)
- Genotypes (BRCA1, BRCA2, PALB2, RAD51B/C/D, HRD/GIS Positive+)
- ER status (Positive, Negative)
- PR status (Positive, Negative)
- HER2 Status:
  - Positive (IHC3+ or IHC2+/ISH+)
  - Low (IHC1+ or IHC2+/ISH-)
  - Negative (IHC0)
- Time from diagnosis of disease to metastasis (months), calculated as (Date of diagnosis for metastatic disease – Date of diagnosis + 1)/30.4375

Conversions for height and weight are as follows:

Height (cm) = Height (inches) x 2.54

Weight (kg) = Weight (lb) x 0.4536

Demographics and baseline disease characteristics will be tabulated and listed in the Safety Population set.

6.1 Prior Anti-Cancer Systemic Therapy

Prior Anti-cancer systemic therapy will be summarized, including

- Prior systemic therapy (Yes, No)
- Number of lines of prior systemic therapy
- Prior platinum
- Prior PARP inhibitor
- Time from the most recent prior systemic therapy to the first dose of the study drug (months), calculated as: (Date of first dose of study drug – End date of last prior systematic therapy +1)/30.4375
- Best overall response (BOR) from last prior systemic therapy

- Reason for therapy ended from last prior systemic therapy (Completion of therapy as planned, Progressive Disease, Toxicity, Other)

Prior anti-cancer systemic therapy will be summarized and listed for Safety Population.

6.2 Prior Anti-Cancer Radiotherapy

Prior Anti-cancer radiotherapy will be listed, including

- Reason for Administration
- Time from most recent radiotherapy to first dose of the study drug (months), calculated as: (Date of first dose of study drug – End date of most recent prior radiotherapy+1)/30.4375

Prior anti-cancer radiotherapy will be listed for Safety Population.

6.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0.

The frequency count and percentage of subjects experiencing any medical conditions will be tabulated by System Organ Classifications (SOC) and Preferred Term (PT). If a Preferred Term or System Organ Class was reported more than once for a subject, the subject would only be counted once in the incidence for that preferred term or system organ class.

Medical history data will be summarized for the Safety Population.

6.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug (WHODrug) Dictionary version March 2024. Unless specified otherwise, summaries of prior and concomitant medications will be presented by Anatomical Therapeutic Class (ATC) Level 2 and Preferred Term with numbers and percentages for subjects in the Safety Population.

A subject who takes more than one medication will be counted only once if these medications belong to the same ATC Level 2 classification.

In the summary tables, prior medications and concomitant medications will be presented by decreasing frequency of subjects overall within each ATC Level 2 class and then similarly by decreasing frequency of subjects overall within each preferred term. In the case of ATC Level 2 classes or preferred terms with equal frequencies, medications will be sorted alphabetically.

Prior medications are defined as those medications that stopped prior to the first administration of the study drug. Concomitant medications/procedures are defined as those medications taken on or after the first administration of the study drug till 30 days after the last dose of study treatment, or the start of subsequent anticancer therapy, whichever occurs first.

A prior medication could also be classified as "both prior and concomitant medication/procedure" if the end date is on or after first dose of study treatment. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

6.5 Concomitant Procedures

Concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. Unless specified otherwise, summaries of concomitant procedures will be presented by System Organ Classifications (SOC) and Preferred Term (PT) with numbers and percentages for subjects in the Safety Population. If a Preferred Term or System Organ Class was reported more than once for a subject, the subject would only be counted once in the incidence for that preferred term or system organ class.

In the summary tables, concomitant medications will be presented by decreasing frequency of subjects overall within each System Organ Class and then similarly by decreasing frequency of subjects overall within each preferred term. In the case of System Organ classes or preferred terms with equal frequencies, procedures will be sorted alphabetically. Transfusions and administration of growth factors will be listed separately.

6.6 Drug Exposure and Compliance

RP-3467 and olaparib (if applicable) exposure will be summarized and grouped by dose level and dose schedule within arm 1 (monotherapy) and arm 2 (combination therapy) respectively, for overall treatment period for the Safety Population by the following parameters for both RP-3467 and olaparib if applicable:

- Duration of treatment (weeks)
- Number of cycles with a non-zero dose
- Any dose interrupted
- Any dose reductions
- Any dose increase
- Actual cumulative dose (in cycle 1 and overall)
- Relative dose intensity (in cycle 1 and overall treatment period)

For duration of treatment (weeks), actual cumulative dose, dose intensity, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided as summary statistics. For dose interruptions and modifications, the frequency and percentage in each category will be provided.

[redacted]

6.6.1 Duration of Treatment

Duration of treatment will be calculated separately for RP-3467 and olaparib. Duration of treatment will be calculated as:

Duration of treatment of RP-3467 or olaparib (weeks) = (min (last dose date of RP-3467 or olaparib respectively; death date; data cutoff date) – treatment start date +1)/7

For participants who have discontinued study treatment, the last dose date will be used as the treatment end date. For participants with ongoing treatment at the time of data extraction, the data cutoff date will be used.

If a participant has a recorded date of death that precedes both the last dose date and the data cutoff date, and it cannot be corrected after querying the issue, the date of death will be used as the treatment end date.

6.6.2 Dose Reduction

Dose reduction is defined as 1) decreased in the total daily dose level or, 2) a decrease in the frequency of dosage (BID to QD for example)

6.6.3 Dose Increase

A dose increase is defined as 1) increase in the total daily dose or, 2) an increase in the frequency of dosage (QC to BID for example). A dose increase may be allowed at the discretion of the Investigator with Sponsor approval. A Participant may be eligible for a dose increase if:

- Completed at least 1 cycle of treatment
- Did not experience any Grade >2 or any significant, unacceptable, or irreversible toxicities considered related to the trial interventions.
- Have not required any prior dose reductions.

All available safety [redacted] data will be used to determine intraparticipant dose escalations. Dose may only be escalated to a level that has been declared safe and tolerable by the SRC. Participants will be annotated with "Intraparticipant dose escalation" and will not be considered part of the DLT-Evaluable population at the dose the participant was escalated to.

[redacted] safety data may be evaluated to increase the frequency of the dose, only after agreement with the SRC.

6.6.4 Actual Cumulative Dose

The actual cumulative dose of RP-3467 or olaparib is defined as the sum of all actual doses administered taking into consideration of any dose change during the study treatment exposure. Information on dose modifications, including dose increases, reductions, and interruptions will be recorded in the CRF. Modifications will be recorded with their start and end dates, as well as the reason for dose change, this information will be used to determine the total cumulative dose over the course of treatment exposure.

6.6.5 Actual Dose Intensity

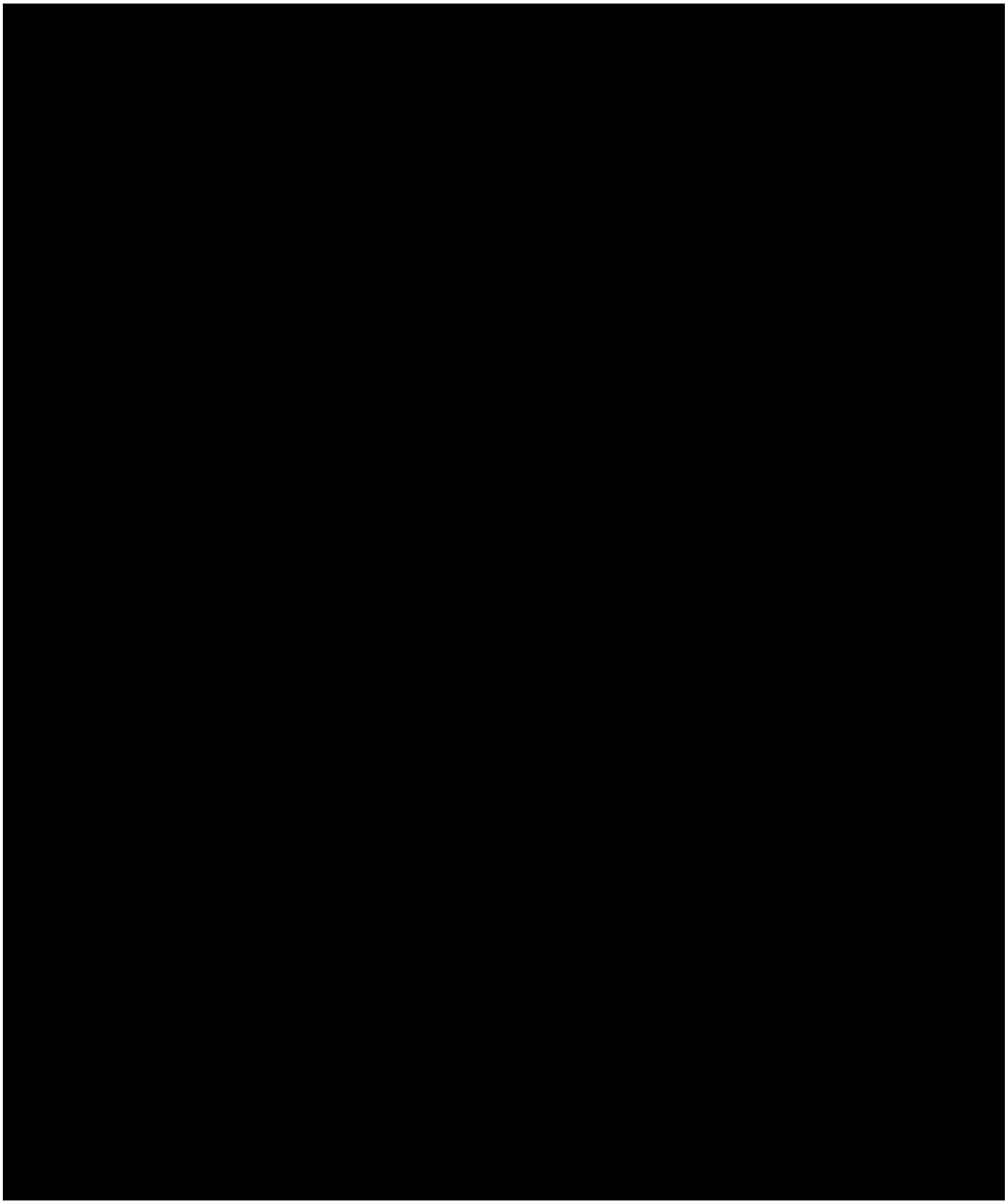
The actual dose intensity (ADI) is defined as the actual cumulative dose during a cycle, calculated only for those patients who started cycle 1 treatment as :

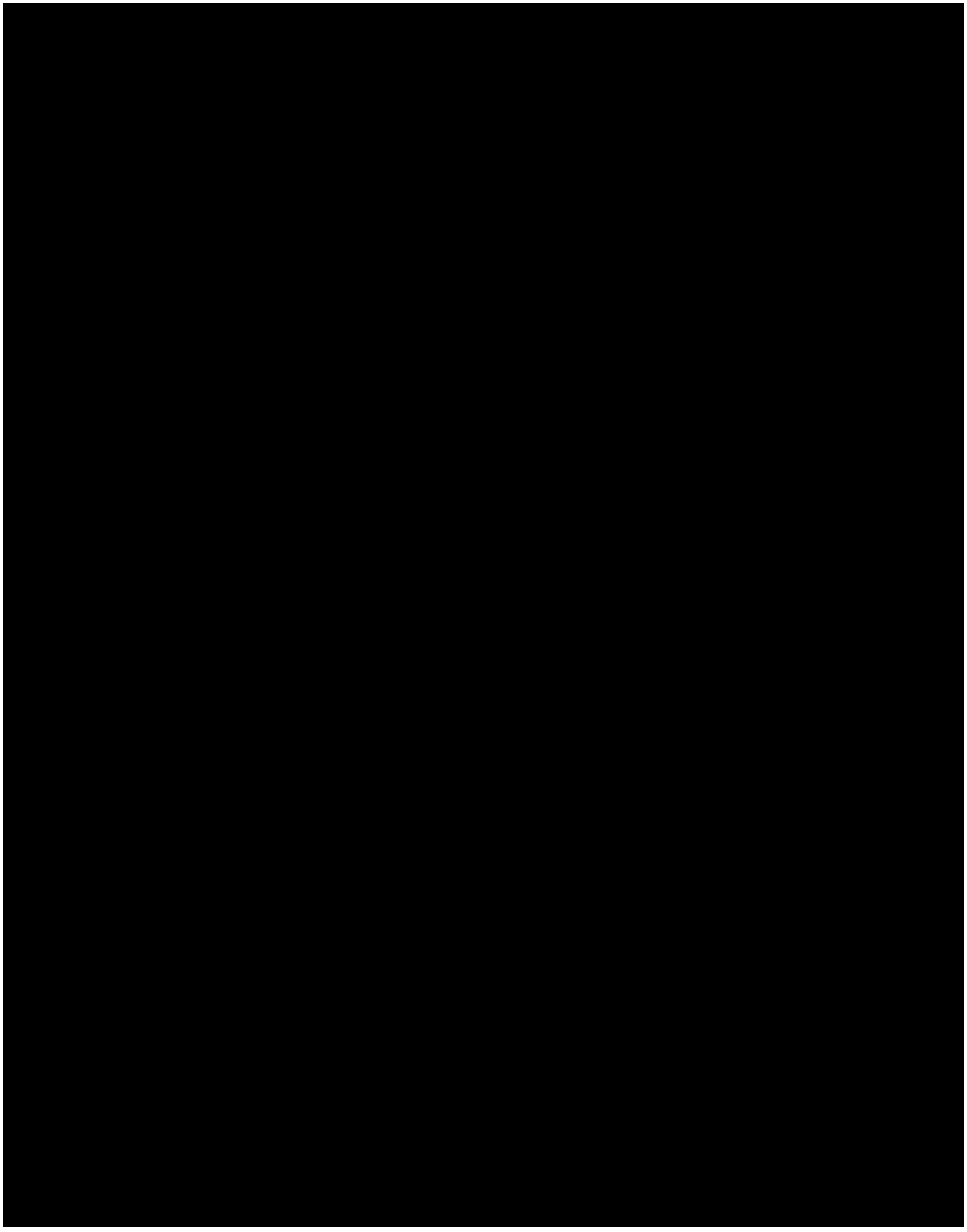
$$\text{RP-3467 or olaparib ADI (mg/cycle)} = \frac{Actual\ Cumulative\ Dose\ (mg)}{\frac{Duration\ of\ exposure\ (days)}{planned\ cycle\ length\left(\frac{days}{cycle}\right)}}$$

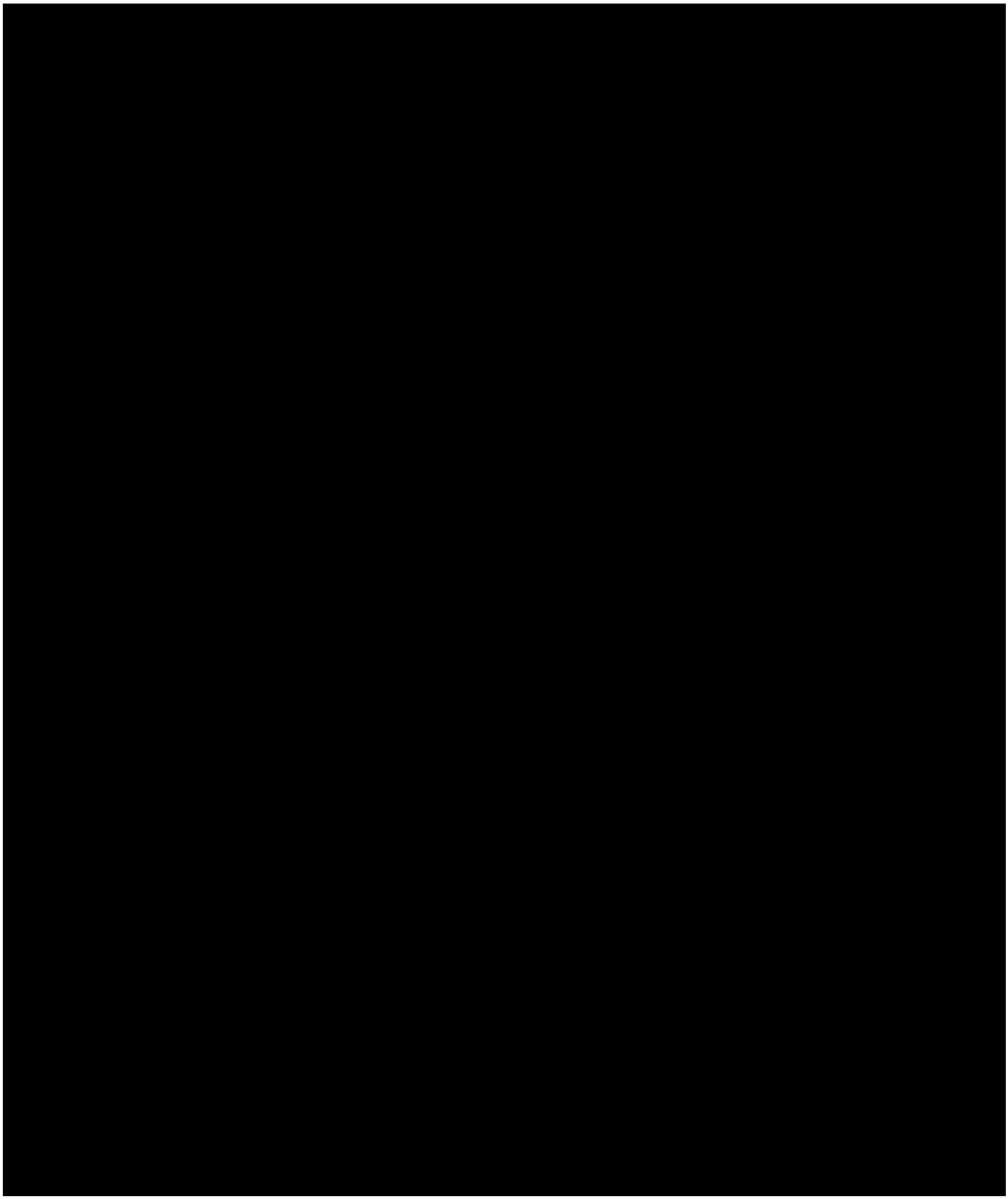
6.6.6 Relative Dose Intensity

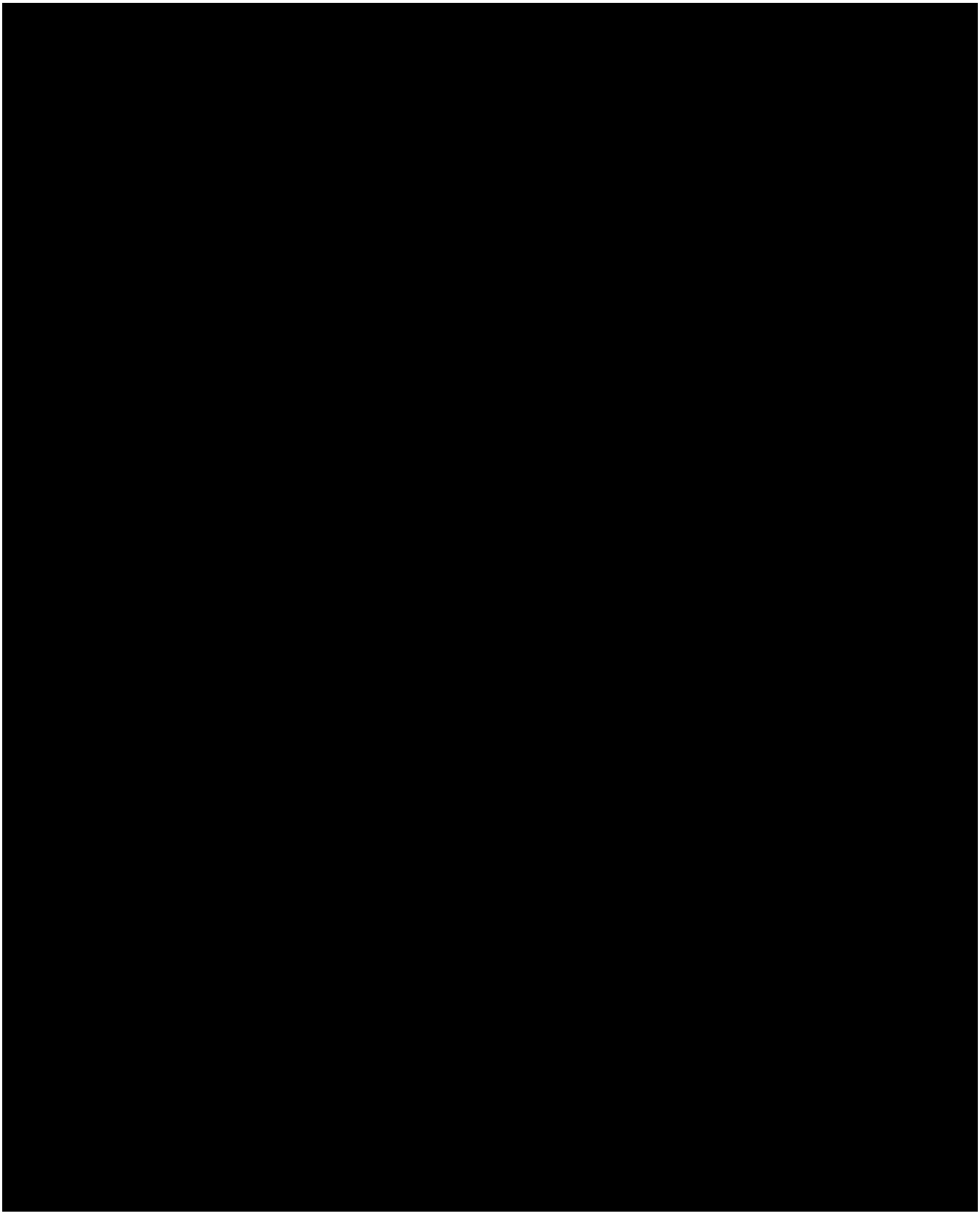
The Relative Dose Intensity (RDI) is defined as the ADI divided by Planned Dose Intensity (PDI) and reported as Percentage. The PDI is defined as the initial dose of the study drug multiplied by planned number of dosing days per cycle according to the protocol. The planned cycle length (days) is 21 days. Initial dose is the dose per day which was intended to be administered at the start of the planned dose regimen. For RDI will be summarized for Cycle 1, as well as across the entire treatment period. Subjects that crossed over from monotherapy to combination therapy, RDI is only calculated up to the start of the rescue treatment period.

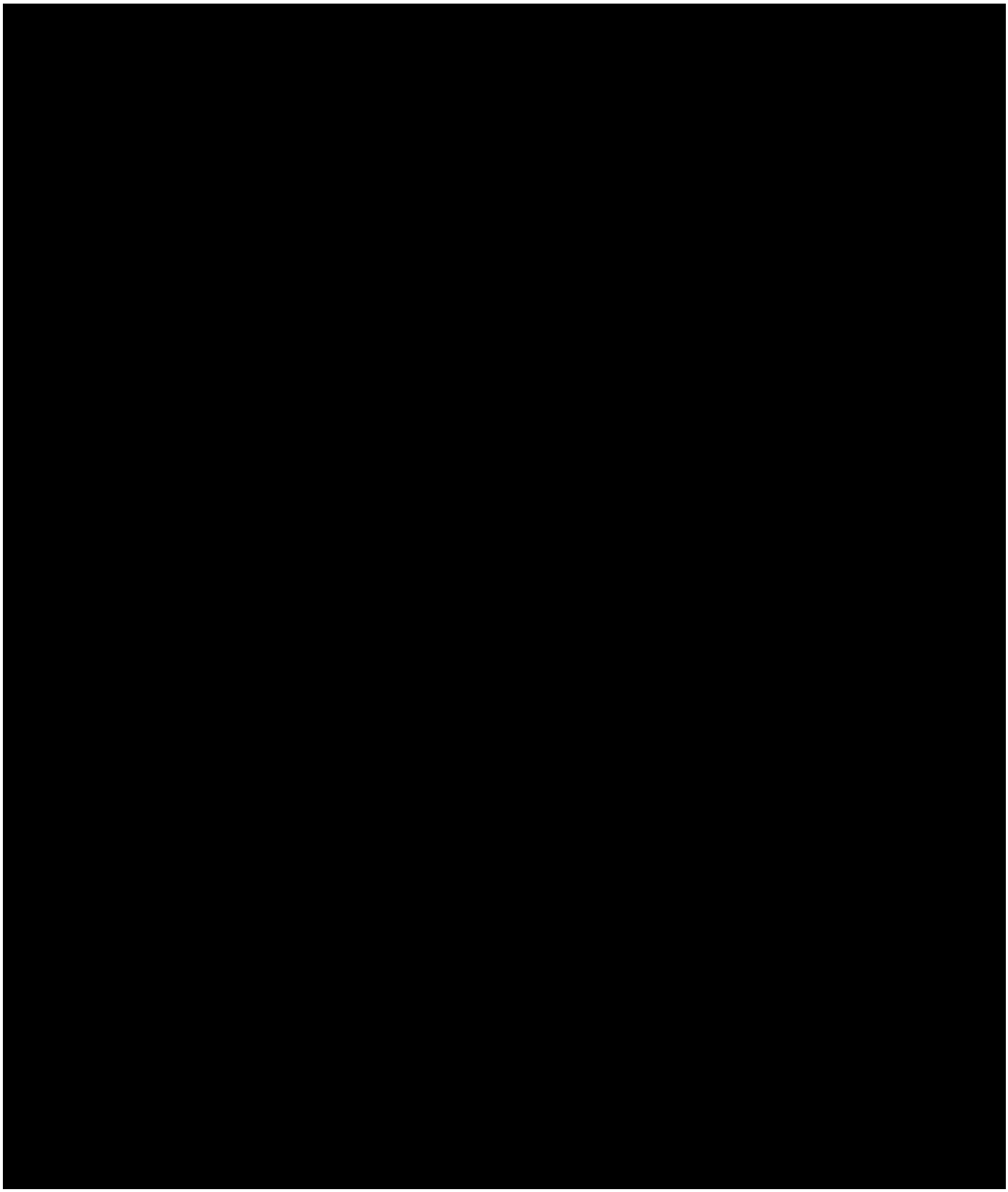
Details of study treatment exposure will be listed for Safety Population and swimmer plot for duration of treatment for individual participants by arm, dose level, and dose schedule will be presented.











10.SAFETY ANALYSIS

10.1 Dose Limiting Toxicities (DLT)

The number of DLTs will be summarized by treatment arms for the DLT Evaluable Population. A toxicity will be considered a DLT if it occurs from the first dose to the end of Cycle 1 [redacted], meets the pre-defined criteria for DLTs, is deemed at least possibly related to trial treatment, and is not clearly and incontrovertibly due to disease progression or extraneous cause. Toxicity will be assessed using CTCAE v5.0, unless other specified. Details of DLTs will be listed.

DLTs will be defined as any of the following:

- Any death not clearly due to the underlying disease or extraneous causes

Hematologic TEAES:

- Grade 4 neutropenia
- Febrile neutropenia (defined as absolute neutrophil count (ANC) <1000 cells/μL with a single temperature of 38.3ºC [100.4˚F] for > 1 hour).
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding.
- Grade 4 anemia or Grade 3 anemia requiring red blood cell (RBC) transfusion given to participants with documented anemia-related symptoms.

Non-Hematologic TEAEs:

- Any Grade ≥ 3 TEAE except the below
    1. Grade ≥ 3 non-hematologic laboratory abnormalities that are asymptomatic and respond to medical intervention or resolve to grade 1 in ≤72 hours.
    2. Grade 3 fatigue with duration < 7 days
    3. Grade ≥ 3 nausea/vomiting/diarrhea that lasts ≤ 72 hours and resolves with or without optimal supportive care.
    4. Grade ≥ 3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis.
    5. The use of red blood cell transfusion for anemia Grade <3 or the use of G-CSF for Grade <4 neutropenia
- Symptomatic Grade ≥ 3 QTc prolongation (QTcF ≥ 501 msec on at least two separate ECGs), or asymptomatic Grade ≥ 3 QTc prolongation that has been confirmed by repeat testing and reevaluation by a qualified person and persists after correction of reversible causes such as electrolyte abnormalities or hypoxia.
- Drug-induced liver injury meeting Hy's Law criteria defined as:
    1. ALT or AST ≥3-fold above the Upper Limit of Normal (ULN) or ≥ 5.0 x ULN in the case of liver metastases at baseline and
    2. Serum total bilirubin ≥ 2-fold above ULN (without findings of cholestasis) and

3. Alkaline phosphatase < 2 x ULN and
4. No other overt reason for liver injury

10.2 Adverse Events

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) with the most current version for the purposes of summarization. NCI CTCAE Version 5.0 will be used for grading AEs. AEs will be collected and recorded for each patient from the day of signing the ICF until 30 days after last trial intervention administration or until participant started alternative anticancer therapy, whichever is sooner. Prior to receiving trial intervention, only AEs considered related to trial procedures and all SAEs will be summarized by arm, dose level, and dose schedule.

A treatment-emergent adverse event (TEAE) will be defined as any event that was not present prior to the initiation of trial intervention(s) or any event that worsens in either intensity or frequency following exposure to trial intervention(s) through 30 days after cessation of trial treatment, or until the participant starts alternate anti-cancer therapy, or the participant is taking the monotherapy treatment and starts the co-therapy olaparib, whichever occurs first. The exception are RP-3467 related SAEs which were reported until the end of trial and will be included as TEAE regardless of time of onset.

All AEs reports will be summarized by treatment regimen (Arm 1 and Arm 2), dose level and schedule (if applicable) unless otherwise specified.

Overall AE summaries will be presented for the Safety Population (unless otherwise specified). The summaries will include the following categories:

- All TEAEs
- TEAEs with CTCAE Grade 3
- TEAEs with CTCAE Grade 4
- TEAEs with CTCAE Grade 5
- DLT (based on DLT evaluable population)
- RP-3467 related TEAE
    - RP-3467 related TEAE with CTCAE Grade 3
    - RP-3467 related TEAE with CTCAE Grade 4
    - RP-3467 related TEAE with CTCAE Grade 5
- Olaparib related TEAE
    - Olaparib related TEAE with CTCAE Grade 3
    - Olaparib related TEAE with CTCAE Grade 4
    - Olaparib related TEAE with CTCAE Grade 5
- Any Serious AEs
- Any treatment-emergent serious AEs (TESAE)
- RP-3467 related TESAEs
- TEAE leading to dose reduction
- TEAE leading to dose interruption
- TEAE leading to study drug withdrawal
- RP-3467 related TEAE leading to dose reduction
- RP-3467 related TEAE leading to dose interruption

- RP-3467 related TEAEs leading to study drug withdrawal
- Olaparib related TEAE leading to dose reduction
- Olaparib related TEAE leading to dose interruption
- Olaparib related TEAE leading to study drug withdrawal
- Adverse Event of Special interest (AESI) if any occurred as defined in the protocol
- TEAE leading to Death

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality will be considered "Related".

Any missing or partial dates will be handled according to the rules outlined in section 5.4.

TEAEs will be summarized by SOC, PT unless stated otherwise. TESAEs, Related TEAEs, TEAEs leading to dose modification, TEAEs leading to drug withdrawn, TEAEs leading to death will be summarized in a similar manner.

Summaries tables will be sorted by decreasing frequency of subjects within each SOC and then similarly by decreasing frequency of subjects within each PT. In the case of equal frequency of number of subjects in SOCs or PTs, summaries will be sorted in descending order. Sorting will be based on the total frequency in the combination therapy arm for safety [redacted] summaries, and across both arms for all other tables, unless stated otherwise.

Myelodysplastic syndrome (MDS) or Acute myelogenous leukemia (AML) are considered AESIs. These are applicable only to participants treated with olaparib will be listed with details if they occur.

If a SOC or PT was reported more than once for a subject, the subject would only be counted once in the incidence for that SOC or PT.

All AEs, SAEs, DLTs, and will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

10.3 Clinical Laboratory Tests

Hematology and serum chemistry parameters will be summarized for Safety population.

For all quantitative parameters, the actual value and the change from baseline will be summarized by dose level and dose schedule (if applicable) for each study visit using descriptive statistics. Both scheduled and unscheduled visits will be considered for baseline derivation.

Laboratory parameters are also graded according to CTCAE v5.0. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value (during the treatment emergent period) according to the NCI-CTCAE grade will be provided for these selected parameters outlined in Table 4. Both scheduled and unscheduled post-treatment visits during the treatment period and up to 30 days past the last dose date will be considered in tabulation of the worst post-treatment value. Additionally, the number and percentage of participants with the following potentially clinically significant abnormal liver function test will be presented. Corresponding listing for patients meeting below criteria:

- ALT >3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST >3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN

Table 4 Laboratory Tests Included in Summary Shift Tables

Category	Parameter	CTCAE Terms
Chemistry	Alanine Aminotransferase	Alanine Aminotransferase increased
	Albumin	Hypoalbuminemia
	Alkaline phosphatase	Alkaline phosphatase increased
	Aspartate Aminotransferase	Aspartate Aminotransferase increased
	Bilirubin	Blood bilirubin increased
	Creatinine	Creatinine increased
Hematology	Hemoglobin	Anemia
	Leukocytes	White blood cell decreased
	Neutrophils	Neutrophil count decreased
	Platelets	Platelet count decreased

10.4 Vital Signs

The observed value and changes from baseline of blood pressure, heart rate, and temperature will be summarized by dose level and dose schedule (if applicable) and by visit for Safety Population.

10.5 12-lead ECG

Descriptive statistics of actual value and change from baseline for ECG parameters including heart rate, PR interval, QRS interval, QT interval, QTc interval, and QTcF interval (Fridericia's corrections) will be presented for baseline visit and scheduled post-treatment visit. The average of triplicate 12-lead ECG results at each timepoint will be used for descriptive statistics. Standard and triplicate 12-lead ECG data will be listed for each participant and time point for the Safety population.

Overall ECG interpretation category (normal, abnormal NCS [not clinically significant], abnormal CS [clinically significant], and not evaluable) is collected in the CRF at baseline and each scheduled post-baseline visit. Shifts tables (shift from baseline to the worst post-baseline values during the treatment emergent period) will be presented.

The QTcF will be categorized into the following categories to identify potentially clinically important changes:

- QTc interval >450 msec and ⩽480 msec

- QTc interval >480 msec and ⩽500 msec
- QTc interval >500 msec

The change from baseline in QTcF will also be categorized separately as follows:

- QTc interval increases from baseline by >30 msec and ⩽60 msec
- QTc interval increases from baseline by >60 msec

For the number of subjects meeting each category for the post-baseline results, the numerator is the number of subjects with meeting the criterion at post-baseline and the denominator is the number of subjects with normal baseline and at least one post baseline assessment in the Safety Population. For the number of subjects meeting each category for the change from baseline, the numerator is the number of subjects with meeting the criterion at post-baseline and the denominator is the number of subjects with baseline and at least one post baseline assessment in the Safety Population.

All ECG tables and listings will be reported on the Safety Population.

10.6 Performance Status

ECOG score will be presented in listings.

11.INTERIM ANALYSIS

Due to the exploratory nature of this Phase 1 trial, data will be assessed descriptively on an ongoing basis after each dose cohort based on safety and clinical activity information to inform the dose selection. No formal statistical inference will be made to these interim evaluations.

12. APPENDIX

Table 5 Schedule of Activities (Arms 1 and 2 [redacted]

	Pre-screening	Screening[a]	[redacted]		Cycle 1						Additional Cycles		EOT Visit[b]	Safety Follow-up[c]	Long-term Follow-up[d]
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	[redacted]	[redacted]	**1**	**2** *(Arm 2 only)*	**8 (+2)[e]**	**9[e]**	**15 (+2)** *(Arm 2 only)*	**17 (+2)** *(Arm 1 only)*	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Pre-screen informed consent	X														
Screening/main informed consent		X													
Inclusion/exclusion criteria		X	[redacted]												

	Pre-screening	**Screening[a]**	[redacted]		**Cycle 1**						**Additional Cycles**		**EOT Visit[b]**	**Safety Follow-up[c]**	**Long-term Follow-up[d]**
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	[redacted]	[redacted]	**1**	**2** ***(Arm 2 only)***	**8 (+2)[e]**	**9[e]**	**15 (+2)** ***(Arm 2 only)***	**17 (+2)** ***(Arm 1 only)***	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Molecular eligibility[h]	X[h]														
Demographics	X														
Medical/cancer history		X													
Physical examination		X											X		
Abbreviated PE			[redacted]								X[i]			X	
Height		X													
Weight		X	[redacted]								X		X	X	
Vital sign measurements[j]		X	[redacted]		X		X		X	X	X	X[g]	X	X	
ECOG performance status		X	[redacted]								X		X	X	
12-lead ECG[k]		X	[redacted]		X[k]		X				X[k]				
Pregnancy test[l]		X	[redacted]								X		X	X	
Chemistry laboratory tests and urinalysis[m]		X	[redacted]								X		X	X	
Hematology tests[m]		X	[redacted]				X		X	X	X	X[g]	X	X	
Serum testosterone[n]		X[n]													
Serum tumor markers[o]		X	[redacted]								X		X		
ctDNA whole blood[p]		X	[redacted]		X[p]						X		X		
Archival tumor tissue[q]		X[q]													
Paired tumor biopsies *(Arm 1 only)*[r]		X[r]								X[r]					

	Pre-screening	Screening[a]	[redacted]		Cycle 1						Additional Cycles		EOT Visit[b]	Safety Follow-up[c]	Long-term Follow-up[d]
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	[redacted]	[redacted]	**1**	**2** ***(Arm 2 only)***	**8 (+2)[e]**	**9[e]**	**15 (+2)** ***(Arm 2 only)***	**17 (+2)** ***(Arm 1 only)***	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Progression Tumor biopsy (optional)[s]													X[s]		
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]				
Tumor assessments[w]		X[x]			*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1. After the first 3 tumor assessments (~5 months/22 weeks on treatment) assessments will be every 9 weeks (±7 days).*										
RP-3467 administration[y]			[redacted]		*See Protocol Section 6.2, Dosage and Administration*										
Olaparib administration[y]					*See Protocol Section 6.2, Dosage and Administration*										
Review of dosing diary[z]					X		X		X	X	X		X		
AE assessment		*During Screening, only AEs considered related to trial procedures or SAEs need to be reported. Following initiation of dosing AE to be collected through 30 days after the last dose of trial intervention or start of new anticancer therapy, whichever is earlier. SAEs believed to be due to trial treatment should be reported through the end of trial date or whenever the Investigator becomes aware thereafter.*											
Concomitant medications/procedures		*To be collected from the time of Screening visit through the Safety Follow-up visit*													
Transfusion and growth factors		*If administered, to be collected from the time of Screening visit through the Safety Follow-up visit*													
Post-trial therapy data collection															X
Survival status															X
Secondary hematologic malignancy status															X

AE = adverse event; BID = twice daily; CA-125 = cancer antigen 15, CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PCWG3 = Prostate Cancer Working Group 3; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event;

WOCBP = women of childbearing potential

a. **Screening:** Screening Period extends from Day -30 to Day -3. Screening laboratory assessments (hematology, chemistry, urinalysis, and serum tumor marker) may be used as Day -2 assessments if performed within 48 hours of the first dose of trial intervention. ECOG performance status and PE that are completed within 24 hours of first dose of trial treatment may be used as Day -2 assessments. Procedures that are to be performed as part of the practice of medicine and which would be done whether or not trial

entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining trial eligibility without first obtaining consent. Participants must continue to meet eligibility criteria prior to the first dose of RP-3467 on Day -2.

b. **EOT Visit:** An End-of-Treatment visit will be conducted following the last dose of trial intervention and within +7 days of the discontinuation of treatment date. If a participant comes to the clinic to start a new cycle but the decision is made to discontinue treatment, that visit may be used as the EOT visit. The EOT visit should occur prior to the start of subsequent anticancer treatment.
c. **Safety Follow-up**: Required for all participants who discontinued from treatment for whatever reason. The window for the Safety Follow-up visit will be 30 (+14) days from the last dose of trial intervention.
d. **Long-Term Follow-Up:** Follow-up will be conducted at approximately 3, 6, 12, 18, and 24 months (±14 days) after the discontinuation of treatment date. This follow-up will be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor. This does not require an in-person visit. Information regarding post-trial therapy, survival status, and hematologic malignancy diagnosis will be collected. The Long-term follow-up period may end sooner if a participant is diagnosed with a hematologic malignancy or if death is known to have occurred prior to 24 months.
e. **C1D8 and C1D9:** A +2 day window is allowed for the C1D8 visit. If a window is used for C1D8, the same window should be used for C1D9.
f. **CXD1:** The start of a new additional cycle should always coincide with the start of trial intervention administration for that cycle. A +3-day window is allowed for the start of new cycles, though cycles should never start early and should be at least 21 days in length. A -2 day window is allowed for the safety assessments scheduled for the CXD1 visit to enable flexibility with visit scheduling.
g. **CXD8:** Hematology and vital signs to be assessed only on Cycles 2 and 3.
h. **Molecular Eligibility:** NGS reports will be emailed to the Sponsor-approved central annotation group for central review to confirm molecular eligibility.
i. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
j. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
k. **ECG:** 12-lead ECGs to be done in triplicate ≥1 minute apart per Table 3 and Table 4 in the study protocol. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. The ECG assessment on C1D1 is for Arm 2 only. For additional cycles, ECG is only to be performed pre-dose on C2D1 and C4D1 and if clinically indicated.
l. **Pregnancy Test:** For WOCBP, a serum pregnancy test is required at Screening. If pregnancy test was done within 48 hours of Day-2, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle, at EOT, and at Safety Follow-up. Pregnancy test can be performed more frequently if required per local regulations.
m. **Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology, and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See protocol Section 8.3.4 for a complete listing of laboratory tests to be performed.
n. **Serum Testosterone:** Required only for participants with prostate cancer without history of bilateral orchiectomy. These participants must have serum testosterone < 50 ng/dL documented during Screening.
o. **Serum Tumor Markers:** This assessment applies *only* to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The screening assessment may be used as the Day -2 assessment as long as this assessment is within 96 hours of C1D1. For participants in Arm 2 the Day -2 assessment may be performed at any date within 96 hours of the dose on C1D1 (as long as it is pre-dose on C1D1).
p. **ctDNA Whole Blood:** The Day -2 collection is for participants enrolled in Arm 1 and the C1D1 collection is for participants enrolled in Arm 2. Blood can be collected either pre- or post-dose for all timepoints except for on Day -2 (Arm 1) or C1D1 (Arm 2), which should be collected pre-dose.
q. **Mandatory Archival Tumor Tissue:** Archival tissue (primary tumor preferred) should be submitted to the Sponsor-designated laboratory during Screening or by C1D1 (+7 days). Refer to Laboratory Manual for further details. If archival tissue does not meet Laboratory Manual specifications, a fresh biopsy can be provided in place of archival tissue. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval.
r. **Paired Biopsies (Arm 1 Only):** Tumor biopsies will be collected during Screening and on C1D17 (+2 days) 1-4 hours post-dose. Participants must have had a minimum of 3 consecutive days of dosing with trial intervention prior to the on-treatment biopsy collection. If biopsy collection at this timepoint is not possible, the Sponsor should be contacted to get approval for collection on an alternative day. Once approved, the participant should have the biopsy as soon as possible after the participant has received at least 3 consecutive days of trial intervention.
s. **Optional Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or prolonged stable disease to evaluate mechanisms of resistance.

[redacted]

w. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (RECIST v1.1) using CT/MRI with contrast of known sites of disease as clinically indicated. A baseline tumor assessment must be performed within 28 days of the first dose. Subsequent assessments must be performed every 6 weeks (±7 days) from C1D1 for the first 3 assessments (~5 months/22 weeks on-treatment), or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ± 7 days during the first ~5 months of trial treatment or every 9 weeks thereafter). For participants with prostate cancer, radionuclide bone scans will be required at baseline and on the same schedule as the RECIST assessments for the assessment of bone disease per PCWG3 criteria. The appearance of new lesions on a bone scan should be confirmed on a subsequent bone scan before determining disease progression based on these results. If a participant

discontinues treatment for a reason other than disease progression, withdrawal of consent to trial, lost to follow-up, or death, the date that radiographic disease progression is next confirmed should be documented if prior to the start of the subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

x. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose.

y. **RP-3467 and Olaparib Administration:** The [redacted] RP-3467 dose should start on a Monday or Tuesday, if unable to accommodate weekend visits.

z. **Review of Dosing Diary:** Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

Table 6 Schedule of Activities (Arm 2[redacted])

	Pre-screening	**Screening[a]**	**Cycle 1**						**Additional Cycles**		**EOT Visit[b]**	**Safety Follow-up[c]**	**Long-term Follow-up[d]**
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	**1**	**2** ***(Arm 2 only)***	**8 (+2)[e]**	**9[e]**	**15 (+2)** ***(Arm 2 only)***	**17 (+2)** ***(Arm 1 only)***	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Pre-screen informed consent	X												
Screening/main informed consent		X											
Inclusion/exclusion criteria		X											
Molecular eligibility[h]	X[h]												
Demographics	X												
Medical/cancer history		X											
Physical examination		X									X		
Abbreviated PE									X[i]			X	
Height		X											
Weight		X							X		X	X	
Vital sign measurements[j]		X	X		X		X	X	X	X[g]	X	X	
ECOG performance status		X							X		X	X	
12-lead ECG[k]		X	X[k]		X				X[k]				

	Pre-screening	Screening[a]	Cycle 1						Additional Cycles		EOT Visit[b]	Safety Follow-up[c]	Long-term Follow-up[d]
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	**1**	**2** ***(Arm 2 only)***	**8 (+2)[e]**	**9[e]**	**15 (+2)** ***(Arm 2 only)***	**17 (+2)** ***(Arm 1 only)***	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Pregnancy test[l]		X							X		X	X	
Chemistry laboratory tests and urinalysis[m]		X							X		X	X	
Hematology tests[m]		X			X		X	X	X	X[g]	X	X	
Serum testosterone[n]		X[n]											
Serum tumor markers[o]		X							X		X		
ctDNA whole blood[p]		X	X[p]						X		X		
Archival tumor tissue[q]		X[q]											
Paired tumor biopsies *(Arm 1 only)*[r]		X[r]						X[r]					
Progression Tumor biopsy (optional)[s]											X[s]		
[redacted]			[redacted]										
Tumor assessments[w]		X[x]	*To be assessed every 6 weeks (±7 days) from Cycle 1 Day 1. After the first 3 tumor assessments (~5 months/22 weeks on treatment) assessments will be every 9 weeks (±7 days).*										
RP-3467 administration[y]			*See Protocol Section 6.2, Dosage and Administration*										
Olaparib administration[y]			*See Protocol Section 6.2, Dosage and Administration*										
Review of dosing diary[z]			X		X		X	X	X		X		
AE assessment		*During Screening, only AEs considered related to trial procedures or SAEs need to be reported. Following initiation of dosing AE to be collected through 30 days after the last dose of trial intervention or start of new anticancer therapy, whichever is earlier. SAEs believed to be due to trial treatment should be reported through the end of trial date or whenever the Investigator becomes aware thereafter.*										

	Pre-screening	Screening[a]	Cycle 1						Additional Cycles		EOT Visit[b]	Safety Follow-up[c]	Long-term Follow-up[d]
Trial Days **Procedures/** **Assessments**	**-180 to -3**	**-30 to -3**	**1**	**2** ***(Arm 2 only)***	**8 (+2)[e]**	**9[e]**	**15 (+2)** ***(Arm 2 only)***	**17 (+2)** ***(Arm 1 only)***	**1 (-2/ +3)[f]**	**8 (+2)[g]**	**Within +7 days of Disc of Trt date**	**30 days (+14) after last dose**	**Up to 24 months after Disc of Trt date**
Concomitant medications/procedures		*To be collected from the time of Screening visit through the Safety Follow-up visit*											
Transfusion and growth factors		*If administered, to be collected from the time of Screening visit through the Safety Follow-up visit*											
Post-trial therapy data collection												X	
Survival status												X	
Secondary hematologic malignancy status												X	

AE = adverse event; CA-125 = cancer antigen 15, CT = computed tomography; ctDNA = circulating tumor DNA; CXDX = Cycle X Day X, Disc of Trt = Discontinuation of treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ICF = informed consent form; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PCWG3 = Prostate Cancer Working Group 3; PE = physical examination; PK = pharmacokinetic; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; WOCBP = women of childbearing potential

a. **Screening:** Screening Period extends from Day -28 to Day -1. Screening laboratory assessments (hematology, chemistry, urinalysis, and serum tumor marker) may be used as Day 1 assessments if performed within 96 hours of the first dose of trial intervention. ECOG performance status and PE that are completed within 24 hours of first dose of trial treatment may be used as Day 1 assessments. Procedures that are to be performed as part of the practice of medicine and which would be done whether or not trial entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining trial eligibility without first obtaining consent. Participants must continue to meet eligibility criteria prior to the first dose of RP-3467 on Day 1.
b. **EOT Visit:** An End-of-Treatment visit will be conducted following the last dose of trial intervention and within +7 days from the discontinuation of treatment date. If a participant comes to the clinic to start a new cycle but the decision is made to discontinue treatment, that visit may be used as the EOT visit. The EOT visit should occur prior to the start of subsequent anticancer treatment.
c. **Safety Follow-up**: Required for all participants who discontinued from treatment for whatever reason. The window for the Safety Follow-up visit will be 30 (+14) days from the last dose of trial intervention.
d. **Long-Term Follow-Up:** Follow-up will be conducted at approximately 3, 6, 12, 18, and 24 months (±14 days) after the discontinuation of treatment date. This follow-up will be conducted by telephone contact or standard method used by participating centers and agreed by the Sponsor. This does not require an in-person visit. Information regarding post-trial therapy, survival status, and hematologic malignancy diagnosis will be collected. The long-term follow-up period may end sooner if a participant is diagnosed with a hematologic malignancy or if death is known to have occurred prior to 24 months.
e. **C1D8 and C1D9:** A +2 day window is allowed for the C1D8 visit. If a window is used for C1D8, the same window should be used for C1D9.
f. **CXD1:** The start of a new additional cycle should always coincide with the start of trial intervention administration for that cycle. A +3-day window is allowed for the start of new cycles, though cycles should never start early and should be at least 21 days in length. A -2 day window is allowed for the safety assessments scheduled for the CXD1 visit to enable flexibility with visit scheduling.
g. **CXD8:** Hematology and vital signs to be assessed only on Cycles 2 and 3.
h. **Molecular Eligibility:** NGS reports will be emailed to the Sponsor-approved central annotation group for central review to confirm molecular eligibility.
i. **Abbreviated PE:** Starting at Cycle 2, abbreviated PE to be performed every 2 cycles (unless full PE necessary by Investigator judgment).
j. **Vital Signs:** Blood pressure, heart rate, and temperature to be measured after the participant has been sitting for 5 minutes.
k. **ECG:** 12-lead ECGs to be done in triplicate ≥1 minute apart per Table 4 in the study protocol. Participants should be in supine position and resting for at least 10 minutes before trial-related ECGs. For additional cycles, ECG is only to be performed pre-dose on C2D1 and C4D1 and if clinically indicated.

l. **Pregnancy Test:** For WOCBP, a serum pregnancy test is required at Screening. If pregnancy test was done within 96 hours of Day 1, repeat testing is not required. A serum or urine pregnancy test must be performed on Day 1 of each cycle, at EOT, and at Safety Follow-up. Pregnancy test can be performed more frequently if required per local regulations.

m. **Safety Laboratory Tests:** Clinical laboratory tests (including serum or plasma chemistry, hematology, and urinalysis) will be performed at local laboratories according to the laboratory's normal procedures. See Protocol Section 8.3.4 for a complete listing of laboratory tests to be performed.

n. **Serum Testosterone:** Required only for participants with prostate cancer without history of bilateral orchiectomy. These participants must have serum testosterone < 50 ng/dL documented during Screening.

o. **Serum Tumor Markers:** This assessment applies *only* to participants with cancers being monitored by circulating tumor markers (e.g., CA-125 or PSA). The screening assessment may be used as the C1D1 assessment as long as this assessment is within 96 hours of C1D1.

p. **ctDNA Whole Blood:** Blood can be collected either pre- or post-dose for all timepoints except for on C1D1, which should be collected pre-dose.

q. **Mandatory Archival Tumor Tissue:** Archival tissue (primary tumor preferred) should be submitted to the Sponsor-designated laboratory during Screening or by C1D1 (+7 days). Refer to Laboratory Manual for further details. If archival tissue does not meet Laboratory Manual specifications, a fresh biopsy can be provided in place of archival tissue. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the participant may still be eligible with prior Sponsor approval.

r. **Optional Post-Progression Tumor Biopsy:** An optional tumor biopsy will be requested post-progression for participants with prior confirmed responses or prolonged stable disease to evaluate mechanisms of resistance.

[redacted]

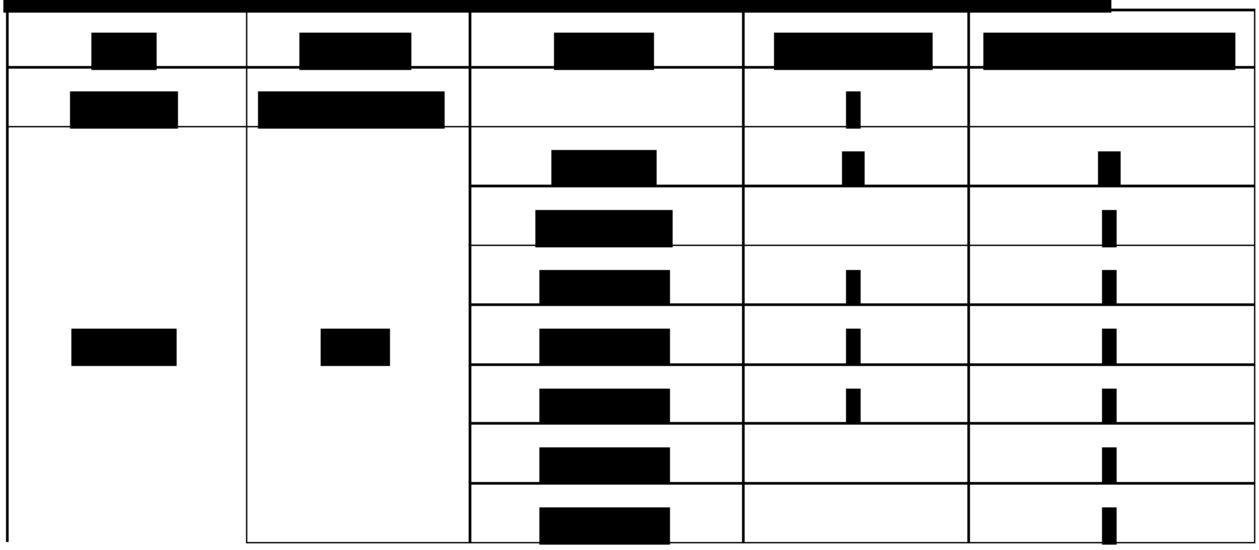
u. **Tumor Assessment:** Tumor assessments by disease-appropriate standard criteria (RECIST v1.1) using CT/MRI with contrast of known sites of disease as clinically indicated. A baseline tumor assessment must be performed within 28 days of the first dose. Subsequent assessments must be performed every 6 weeks (±7 days) from C1D1 for the first 3 assessments (~5 months/22 weeks on-treatment), or sooner if clinically indicated). Thereafter, assessments must be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response or partial response should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ± 7 days during the first ~5 months of trial treatment or every 9 weeks thereafter). For participants with prostate cancer, radionuclide bone scans will be required at baseline and on the same schedule as the RECIST assessments for the assessment of bone disease per PCWG3 criteria. The appearance of new lesions on a bone scan should be confirmed on a subsequent bone scan before determining disease progression based on these results. If a participant discontinues treatment for a reason other than disease progression, withdrawal of consent to trial, lost to follow-up, or death, the date that radiographic disease progression is next confirmed should be documented if prior to the start of the subsequent anticancer treatment. All radiographic images/scans at the timepoints specified as well as any unscheduled images/scans should be archived by the trial sites for potential future evaluation.

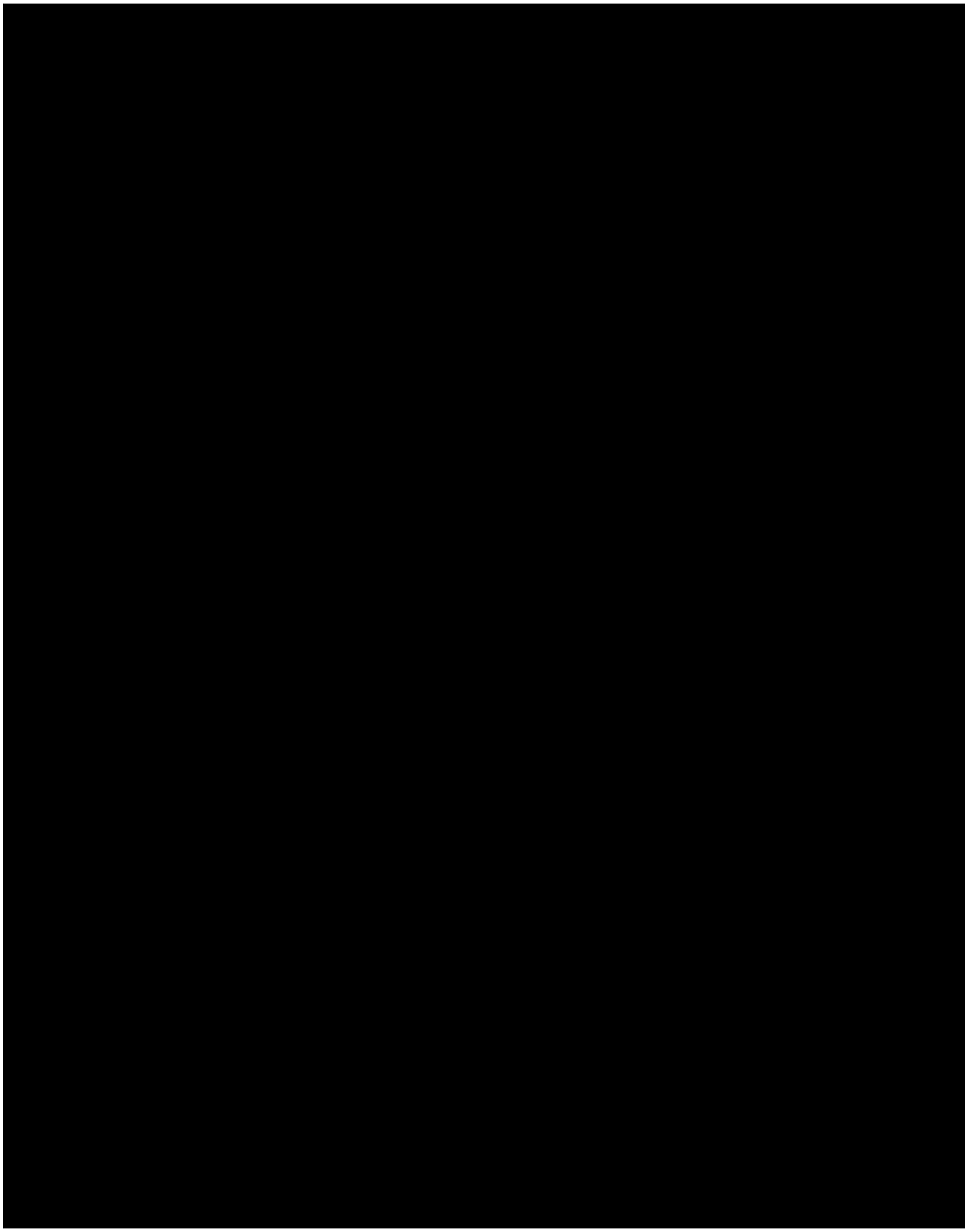
v. **Tumor Assessment at Screening:** Scans performed prior to signing of the ICF as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and performed within 28 days prior to the first dose.

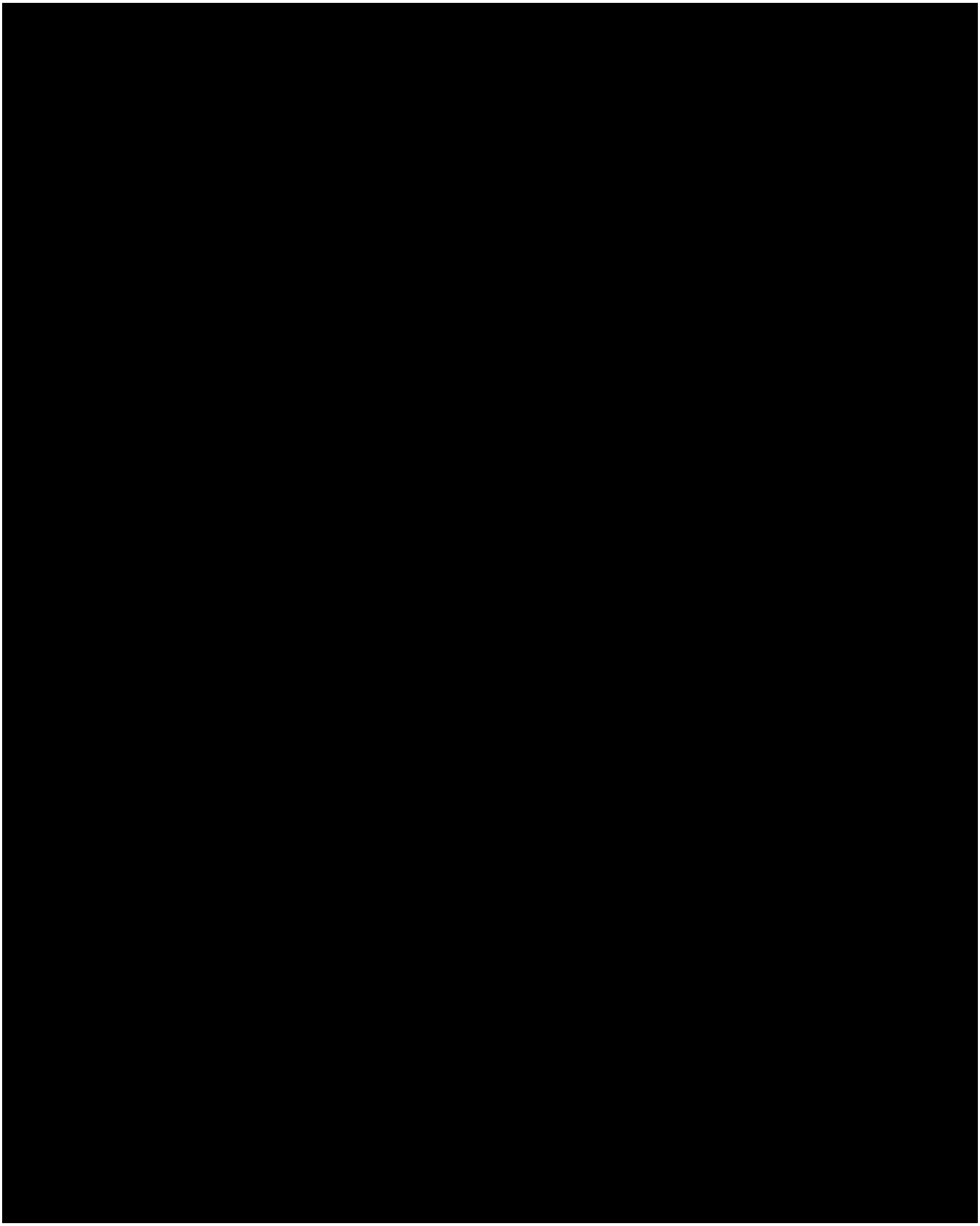
w. **RP-3467 and Olaparib Administration:** Dosing should start on Monday through Thursday if unable to accommodate weekend visits.

Review of Dosing Diary: Dosing diary will be reviewed at each participant visit and collected at each CXD1 visit and at EOT. Additional details are in the Pharmacy Manual.

[redacted]







[redacted]

12.1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on trial). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8: For Participants with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	>4 wks. Confirmation[b]
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation[b]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once 6 wks. from first dose of trial intervention[b]
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD[c]	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

a. See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.
b. Only for non-randomized trials with response as primary endpoint.
c. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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 the objective progression even after discontinuation of treatment.

Table 9: For Participants with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	not evaluated

Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; SD = stable disease

a. Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

12.1.2 Response Evaluation Based on Prostate Cancer Working Group 3 Criteria

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) are outlined in Section 12.1.1 and will be utilized for evaluation of response in participants with prostate cancer with measurable and non-measurable disease involving soft tissue lesions. A modification from standard RECIST v1.1 is that bone lesions will not be recorded as target or non-target lesions for the assessment.

In addition to RECIST v1.1, participants with prostate cancer will be evaluated by the Prostate Cancer Working Group (PCWG3) criteria for assessment of bone progression and prostate-specific antigen (PSA) response as described by Scher 2016.

Bone Lesions

The presence or absence of bone metastasis will be assessed at baseline by ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy. The total number of bone lesions will be recorded.

Assessment for progression:

- A minimum of two or more new lesions compared with the baseline bone scan after the 12-week flare window.
- If the new lesions occur within the first 12 weeks of treatment, assessment of progression requires a confirmatory scan performed 6 or more weeks later showing two additional new lesions compared with the first follow-up scan to rule out pseudoprogression (2 + 2 rule).
- If at least two additional new lesions are seen on the next (confirmatory) scan performed after the 12-week flare window, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented.
- Changes in intensity of uptake alone do not constitute either progression or regression.

PSA

For participants with nonmeasurable disease, PSA measurements will be used to assess response. To be evaluable for PSA response PSA levels must be > 2 ng/mL at the most recent assessment and must be rising as determined by a sequence of increasing values at a minimum of 1-week apart prior to treatment start.

Assessment for response:

- Confirmed PSA response is defined as ≥ 50% reduction in PSA from baseline to lowest post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later.

Assessment for progression:

- PSA progression is defined as a PSA increase ≥ 25% and ≥ 2g/mL above the nadir (or baseline for participants who did not have a decline in PSA), confirmed by a second increasing value at least 3 weeks later.

- A PSA rise within the first 12 weeks of therapy in the absence of evidence of confirmed radiologic progression will not be used as a criterion for progression.

12.1.3 Gynecological Cancer Intergroup Definitions for Response and Progression in Participants with Ovarian Cancer

For participants with ovarian cancer with elevated CA-125 levels, response evaluation will include cancer antigen 125 (CA-125) in addition to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria as per Gynecological Cancer Intergroup (GCIG) criteria (Rustin 2011).

Definition of Response by CA-125

- A ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 3 weeks (note that GCIG recommends maintenance for at least 28 days; a modification was made based on the 3-week cycle length in this trial). Participants can be evaluated for a CA-125 response only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within two weeks before starting treatment.

- Intervening samples and the confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%).

- The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.

- A CA-125 complete response can occur if CA-125 levels fall to within the reference range.

Definition of Progression by CA-125

- For participants with elevated CA-125 pre-treatment that normalizes or for participants with CA-125 in the normal range at baseline: CA-125 at least 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

- For participants with elevated CA-125 pre-treatment which never normalizes: CA-125 at least 2 times the nadir value on 2 occasions at least 1 week apart.

- Progressive disease (PD) by objective change in tumor size should always take precedence over changes in CA-125 should it occur first. If measurable disease is reducing in size but the CA125 suggests progression the participant should remain on treatment.

- CA-125 progression will be assigned the date of the first measurement that meets the above criteria.

Note: CA-125 progression in the absence of radiographic or other clinical evidence of progression will not be sufficient criteria for treatment discontinuation in this trial.

Participants are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

Evaluation of Best Overall Response by Combined CA-125 and RECIST 1.1 Criteria

- If participants have a CA-125 response but have PD by RECIST within 28 days of the CA-125 response, they will be classified as PD.

- Participants whose best response by RECIST is stable disease (SD) but who have a CA-125 response will be classified as CA-125 responders

- For a participant to be classified as a complete responder according to RECIST, CA-125 levels must be within the normal range

Table 12: For Participants with Measurable Disease

Target Lesion*	Nontarget†	New Lesion	CA 125	Overall Best Response	
CR	CR	No	Normal	CR	Best RECIST 1.1 response for CR and PR also requires it to be confirmed and maintained for at least 28 days if response is primary end point
CR	Non-CR Non-PD	No	Not PD	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-PD or NAE	No	Not PD	PR	
NAE	Non-PD	No	PR	PR	
PD or New >28 days from CA 125 PR‡			PR	PR	
SD§	Non-PD	No	PR	PR	
SD§	Non-PD or NAE	No	Not PR and not PD	SD	
PD or New ≤28 days From CA 125 PR‡			PR	PD	
PD	Any	Yes or No	Any	PD	
Any	PD	Yes or No	Any	PD	
Any	Any	Yes	Any	PD	
Any	Any	Yes or No	PD	PD	

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.
†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
‡Patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA 125 response.
§The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

Table 13: For Participants Without Measurable Disease

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

13.REFERENCE

Eisenhauer EA, et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 45(2), 228-47.

Park, J. R., et al. (2017). Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 35(22), 2580–2587.

Rustin, G. J., et al. (2011). Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 21(2), 419–423.

Scher, H. I., et al. (2016). Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 34(12), 1402–1418.