Statistical Analysis Plan

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Phase 1/2a Study of the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Clinical Activity of RP-3500 Alone or in Combination with Talazoparib or Gemcitabine in Advanced Solid Tumors with ATR Inhibitor Sensitizing Mutations (TRESR Study)

Statistical Analysis Plan for RP-3500-01

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
AE	Adverse event
ADaM	Analysis data model
ALT	Alanine aminotransferase
AR	Accumulation ratio
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated
ATRi	Ataxia telangiectasia-mutated and rad3-related inhibitor
CA-125	Cancer antigen 125
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DCO	Data cut off
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCIG	Gynecological Cancer Intergroup
Geom CV	Geometric coefficient of variation
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational new drug
[redacted]	[redacted]
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximal tolerated dose
NGS	Next generation sequencing

Abbreviation or Special Term	Explanation
NQ	Nonquantifiable
OR	Odds ratio
ORR	Objective response rate
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PE	Physical exam
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PSA	Prostate-specific antigen
PT	Preferred term
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	Système International
SOC	System organ class
SDTM	Study data tabulation model
SRC	Safety review committee
TEAE	Treatment-emergent adverse event
TL	Tumor lesion
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Version	Brief Description of Major Changes
2.0	• Added Modules 4 [redacted] and modified Module 2 based on Protocol Version 6.0 • Definition of treatment-emergent adverse event was changed to end at 30 days of last dose or up to time of crossover to a new module • Primary efficacy population for Module 2 (Phase 2) updated to be consistent with the Protocol Version 6.0 • Primary efficacy population for Phase 1 modules (Modules 1, 3, 4 [redacted]) updated to include patients with at least 1 postbaseline tumor assessment or evaluable for tumor markers, due to exploratory nature of Phase 1 modules • Added a new endpoint to assess clinical benefit based on radiographic and tumor marker response, and duration of treatment criteria • Overall response endpoint added based on any radiographical response by Response Evaluation Criteria in Solid Tumors version 1.1 [redacted] or confirmed tumor marker (prostate-specific antigen [PSA] or CA-125) response • Additional details were added to derive the efficacy endpoints (e.g., progression-free survival) • Added PSA and CA-125 as endpoints for assessment of anticancer treatment efficacy based on Gynecological Cancer Intergroup (GCIG) and Prostate Cancer Clinical Trials Working Group 3 criteria • Added a summary table of sample size for each module • Added summary for postbaseline categories of liver function tests and vital signs • Revised analyses on baseline disease characteristics and other safety endpoints • Revised the biomarker analyses based on updated protocol. Analysis by zygosity was added • Modified the calculation of dose intensity to handle missing data • Updated Section 5.3.1 based on data handle convention of missing or incomplete data • Dose Response Modeling section was removed from SAP • Added appendix for GCIG (ovarian) criteria
3.0	• Updated number of planned patients to be enrolled in the study from approximately 457 to approximately 451: Module 2 Arm 2 is closed to further enrollment and that expansion cohorts (2 cohorts, 8 patients each was planned) will no longer be considered; Added a low dose gemcitabine arm (Arm 2) to Module 4 and enrollment estimates for Module 4 increases to 70 patients from 40 patients [redacted]

	• Updated efficacy population definitions for Module 1 based on clinically relevant dose levels, incorporate information from the pharmacodynamic/pharmacokinetic (PK) analyses • Due to early discontinuation of enrollment in Module 2, the primary objective of this module will not be assessed. The limited patients enrolled in Module 2 will be combined with Module 1 patients to better evaluate Module 1 objectives with monotherapy treatment • Efficacy Population 1 was renamed to Efficacy Evaluable Population for monotherapy treated patients (Module 1+2). • Efficacy Population 2 was removed because it was the primary efficacy population defined for Module 2 only • Primary Efficacy Population for monotherapy was added for patients treated >100 mg/day based on preclinical PK finding to obtain a more accurate efficacy measure under this efficacious exposure. • Restriction of at least one post baseline tumor assessment was added to all efficacy population definitions • [redacted] • Definition 2 of clinical benefit rate (CBR) was removed based on the updated definition of CBR in Protocol Amendment 6.0 (v7.0). CBR endpoint was updated in efficacy endpoints • Section 5.1 General Principle on the format of summary of the data was updated given that Module 2 patients will be combined with Module 1 patients • Safety Narrative Criteria was updated • Added Appendix 3 Response Evaluation Based on Prostate Cancer Working Group 3 Criteria
4.0	• Updated the SAP based on Protocol v8.0 (21 Jun 2024) • Overall survival was removed per protocol • Updated the definition of Efficacy Population • Updated the definition of TEAE • Added rule for derivation of confirmed responses in Appendix 1

1 INTRODUCTION

This statistical analysis plan (SAP) prospectively describes the planned analyses for the study, protocol RP-3500-01 (IND #146280). The SAP is written based on Protocol Version 8.0 (21 Jun 2024) and is in full conformity with the most current version of Good Clinical Practice, the Food and Drug Administration (FDA) and International Council for Harmonisation (ICH) guidelines for clinical trials. Any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. In addition, the datasets generated for this study will be fully compliant with the latest version of the Clinical Data Interchange Standards Consortium standards for the study data tabulation model (SDTM) and analysis data model (ADaM) datasets.

This SAP covers the primary and secondary objectives of the study. [redacted] In addition, population pharmacokinetic (PK) and PK/pharmacodynamic modelling will be addressed outside of the SAP.

2 STUDY DETAILS

2.1 Changes to the Protocol Defined Statistical Analysis Plan

Major changes in analysis from protocol planned analysis:

- Primary efficacy population for Module 1+2 patients is added to assess antitumor activity in patients treated with >100 mg/day dose. Dose level of >100 mg/day was predicted to achieve efficacious exposure based on preclinical data indicating that optimal antitumor activity was achieved at more than 6 hours of IC80 coverage with acceptable long term tolerability

- The original efficacy population definition from the protocol was renamed to Efficacy Evaluable Population for assessment of antitumor activity in all dose levels

- Definition of efficacy population was updated to clarify requirements to be efficacy evaluable

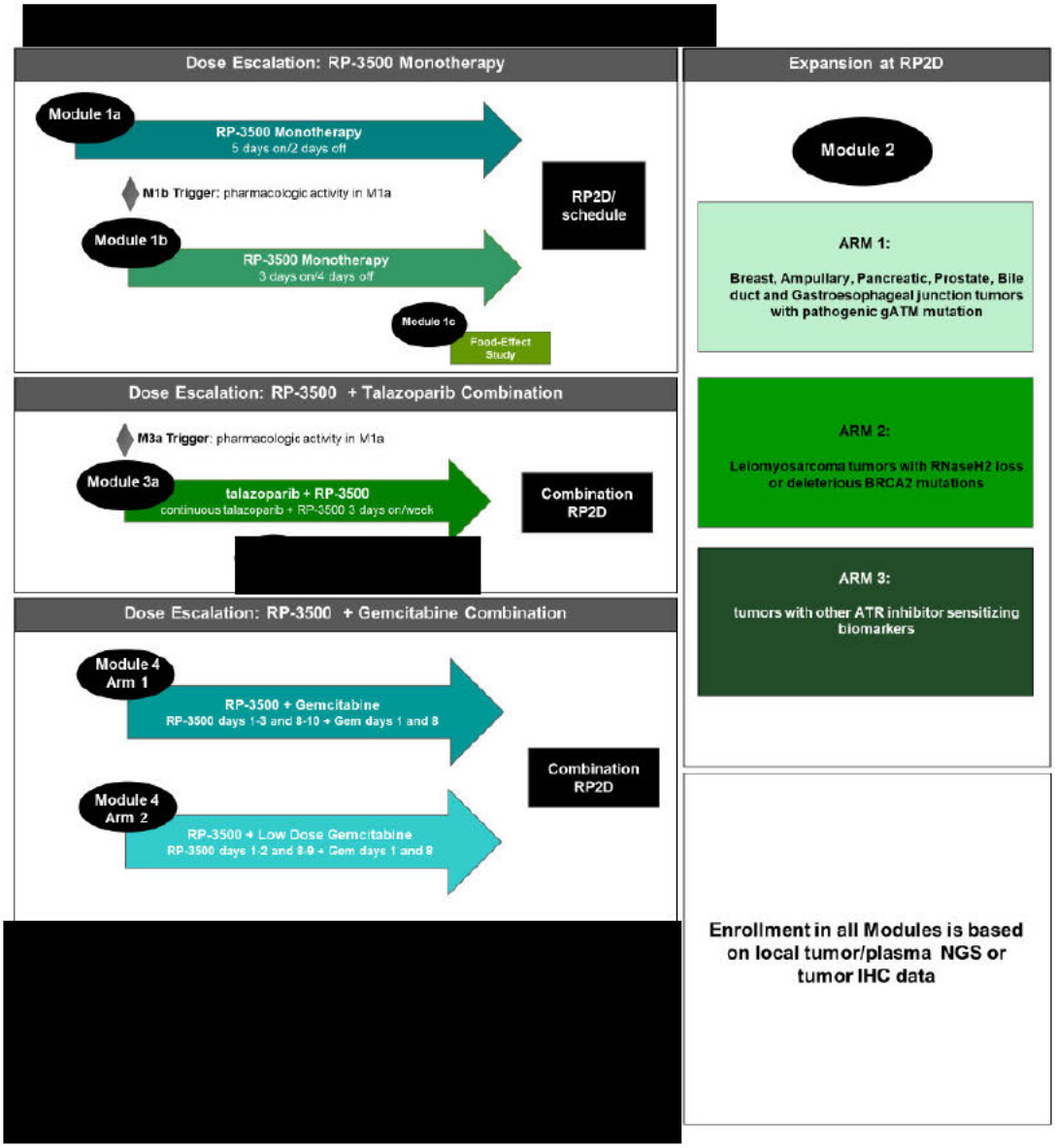
- Given the early termination of Module 2 and limited number of patients enrolled in this module, Module 1 and Module 2 patients will be combined for assessment of safety and antitumor effect for the monotherapy, based on Module 1 objectives. Planned Module 2 specific analyses will not be performed, including time to prostate-specific antigen (PSA) progression originally planned for Module 2 patients with prostate cancer

2.2 Study Design

This is an exploratory modular, Phase 1/2a, first-in-human, multicenter, open-label, nonrandomized, dose escalation, and dose-expansion study of RP-3500 administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors.

Patients will be enrolled based on center-specific routine genomic and immunohistochemistry (IHC) tests able to detect alterations in genes associated with ataxia telangiectasia-mutated and rad3-related inhibitor (ATRi) sensitivity. In Modules 1-4, approximately 451 patients are expected to be enrolled at approximately 20 sites globally [redacted] No patients were enrolled in this

module. As of 31 October 2022, enrollment in Module 2 was prematurely discontinued per Sponsor decision. A total of 20 patients were enrolled out of 191 planned for Module 2.



Eligible patients will be enrolled into Module 1 (approximately 140 patients), RP-3500 monotherapy dose escalation, evaluating the safety, tolerability, PK, and food effect of RP-3500 administered using 2 schedules. The study will continue with the initiation of Module 3 (up to 50 patients), RP-3500 and talazoparib combination, after a dose level that demonstrates pharmacologic activity is observed in Module 1a. Evidence of pharmacologic activity can include grade ≥2 drug-related toxicity at any cycle, PK data demonstrating exposure levels predicted to be efficacious based on nonclinical studies, or other evidence of treatment-related activity as agreed on by the safety review committee (SRC). Module 2 enrollment will proceed once the RP-3500 monotherapy recommended Phase 2 dose (RP2D) and recommended preliminary dosing schedule are determined in Module 1.

Module 2 aims to explore the preliminary efficacy of RP-3500 in patients whose tumors harbor an ATRi sensitizing biomarker. Module 2 will include 3 arms:

- ARM 1: ER+/HER2- breast, ampullary, pancreas, prostate, bile duct or gastroesophageal junction tumors with likely pathogenic/pathogenic germline ataxia telangiectasia mutated (ATM) gene mutations

- ARM 2: leiomyosarcomas with either RNASEH2 loss or deleterious/likely deleterious BRCA2 mutations. As of Protocol Amendment 6.0, Module 2 Arm 2 has closed for further enrollment
- ARM 3: tumors with other ATRi sensitizing biomarkers: ATRIP, CHTF8, FZR1, MRE11, NBN, RAD17, RAD50, RAD51B/C/D, REV3L, SETD2, and other genes agreed upon between the Sponsor and investigator

Module 3 will assess the safety and tolerability of RP-3500 in combination with talazoparib and evaluate the preliminary efficacy of the combination. Module 4 will evaluate the safety and tolerability of RP-3500 in combination with gemcitabine. [redacted]

In all modules, patients will be enrolled based on locally assessed tumor, germline, or plasma next generation sequencing (NGS) results or IHC data generated in a College of Pathology/Clinical Laboratory Improvement Amendments-certified laboratory (International Organization for Standardization or equivalent) following center-specific institutional guidelines.

The local NGS and IHC reports will define the biomarker status for both enrollment and for the primary efficacy analysis of clinical response to RP-3500. Subsequently, the Sponsor will independently confirm local test results with centralized NGS when adequate tissue is available. Centralized testing results will be used to confirm the local results and exploratory analyses.

2.3 Schedule of Assessments

See protocol for full details on the schedule of assessments for the different modules.

The study will consist of a Prescreening Period (within 6 months from time of enrollment), Screening Period (Day -28 to Day -1, to determine eligibility), Treatment Period, an End-of-Treatment (EOT) Period (occurring 30+7 days after the last dose of study drug or 7 days after the last dose of study drug if discontinued due to a treatment-related toxicity), and a Survival Follow-Up Period (every 3 months [±2 weeks] for 1 year after the last dose of study drug). Survival follow-up was shortened from 12 months to 3 months in Protocol v8.0 (21 Jun 2024). The treatment period will consist of 21- or 28-day cycles.

The key assessments/study procedures required in this study include:

- Tumor assessments (based on computed tomography [CT] and/or magnetic resonance imaging scan) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Positron emission tomography (PET)/CT may be administered as clinically indicated. For patients with prostate cancer in Module 2, radionuclide bone scans will also be performed
- PK samples throughout the study
- Baseline, on-treatment, and end-of-treatment blood samples
- Reporting adverse events (AEs) occurring from the day of signing the main study informed consent form
- Pretreatment tumor biomarker data
- Archival tumor tissue
- [redacted]
- Electrocardiograms (ECGs) and vital signs

Multiple procedures may be scheduled at the same timepoint relative to RP-3500 dosing.

2.4 Sample Size Considerations

The sample sizes for all the modules are listed in Table 1 below.

Table 1 Planned Sample Size for Each Module

Module	Sample Size
Dose Escalation Modules	
Module 1	Up to 140
Module 1c	12 (included in 140 above)
Module 3	50
Module 4	70
[redacted]	
Dose Expansion Module	
Module 2	Total up to 191
Initial sample size	143 (Arm 1: 42, Arm 2: 21, Arm 3: 80)
Expansion cohorts	Up to 48 (6 expansion cohorts)

2.4.1 Module 1 Sample Size

The maximum total number of patients exposed for Modules 1 will be 140. The numbers of patients in Module 1 will depend on the number of dose escalations and include up to 8 patients enrolled in any of the backfill cohorts. The initial number of planned patients to be treated in Module 1 was increased from 80 to 140 to enable testing of additional treatment schedules involving intermittent weekly dosing schedules and to further evaluate PK/pharmacodynamic/efficacy relationships in tumors with specific genomic abnormalities.

The sample size for Module 1c will be a total of approximately 12 patients, based on FDA guidelines for similar single-dose, food-effect, crossover studies for PK determinations (CDER 2019).

2.4.2 Module 2 Sample Size

The maximum number of patients included in the assessment of efficacy in Module 2 will be 191. This will consist of an initial sample size of 143 patients across 3 different arms and genotype subsets (Arm 1: 42 patients, Arm 2: 21 patients, Arm 3: 80 patients), followed by potentially up to 48 patients from 6 cohort expansions based on the observation of efficacy in specific tumor types/genotypes. The final number of patients enrolled in Module 2 will also be determined by the number of patients enrolled in any of the expansion cohorts. Arm 1 may include up to 3 expansion cohorts, and Arm 3 up to 3 expansion cohorts (up to 8 patients each).

The planned sample size for Arm 1 and Arm 2 is based on achieving 80% power for a target response rate under a 2-stage design (Table 2). The planned sample size of up to 80 for Arm 3 is based on the estimated sample size of 5 to 8 patients for each of the 8 genotype subsets to be evaluated in Arm 3, with the intention of identifying signal of activity for further selection.

The criteria for rejecting the null hypothesis (H0: response rate = p0) for Arm 1 and Arm 2 based on the preliminary efficacy endpoint of overall response rate as well as the futility

criteria based on interim data are described in Table 2. Note the sample size in the table does not include patients in the expansion cohort.

Table 2 Module 2 Efficacy Cohort Success and Futility criteria for Arm 1 and Arm 2

Arm	Total N	Success Criteria	p0	p1	Futility n	Futility Criteria	Pet-p0
1	42	≥8/42 (19%)	0.10	0.25	14	≤1/14 (7%)	0.58
2	21	≥5/21 (24%)	0.10	0.32	11	≤1/11 (9%)	0.70

n = number of patients required for assessment of futility; N = total number of patients required for the final analysis if futility criteria is not met; OR = overall response; p0 = the null hypothesis for OR, the minimal level of efficacy required; p1 = the alternative hypothesis for OR, the desired level of efficacy; Pet-p0 = probability of early termination with a true OR of p0.

Success criteria are defined as the total number of responses (having either a complete response [CR] or partial response [PR] or tumor marker response) required to reject the null hypotheses at the final analysis. The futility criteria are defined as the total number of responses that would lead to cessation of enrollment in that cohort. The interim futility analysis will be performed when the initial number of evaluable patients (interim n in Table 2) have completed 4 months of follow up or have discontinued the study treatment. The evaluable patients will be those in efficacy population.

Both Arm 1 and Arm 2 sample size was based on achieving 80% power with 1 sided alpha of 5%, utilizing a 2-stage design. The specific 2-stage designs selected minimize both the number of patients recruited for the futility and final analyses, with each design closely resembling either an Optimal or MiniMax design.

The number of patients in each arm was determined by hypothesized efficacy specific to each arm that would warrant further development. Based on the rejection of a null hypothesis for a minimal response rate, cohort-specific success criteria are defined in terms of the number of responses needed to be observed, from the required number of patients. In addition, futility criteria are defined which require a minimal level of response to be observed so that cohorts are fully enrolled.

2.4.3 Module 3 Sample Size

The maximum number of patients enrolled across Modules 3 will be 50.

Module 3 may begin at the earliest after a dose level that demonstrates pharmacologic activity (grade ≥2 drug-related toxicity at any cycle, PK data demonstrating exposure levels predicted to be efficacious based on nonclinical studies, or other evidence of treatment-related activity as agreed on by the SRC) has been identified in Module 1a. The Module 3a starting dose will be 1 dose level below the highest evaluated daily dose in Module 1a. Module 3 will start with cohorts of 3 to 4 patients.

[redacted]

2.4.4 Module 4 Sample Size

The number of patients enrolled across Module 4 will be approximately 70.

Module 4 will include 2 arms. Arm 1 will study gemcitabine dose ranges of 400 to 1000 mg/m^2 with RP-3500. Arm 2 will be a low dose gemcitabine arm that will evaluate gemcitabine doses of 100 to 300 mg/m^2 in combination with RP-3500.

Backfill cohorts (up to 8 patients each) may be employed based on agreement with the SRC. The objectives of the backfill cohorts are to:

1. Aid in the assessment of possible antitumor activity in a subset of patients with a specific genomic abnormality or tumor type
2. Further assess drug combination-related toxicities

[redacted]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Module 1 Objectives

Objective(s)	Endpoint(s)
Primary	
To assess the safety and tolerability of RP-3500 in patients with eligible advanced solid tumors	AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, and ECGs evaluations
To define the maximum tolerated dose (MTD) of RP-3500 monotherapy, and determine a recommended Phase 2 dose (RP2D) and schedule	DLTs Safety and tolerability (as described above)
Secondary	
To assess preliminary antitumor activity with RP-3500 in patients with eligible advanced solid tumors	Objective response rate (ORR), overall response rate based on ORR and tumor marker response, duration of response (DOR), clinical benefit rate (CR, PR, or tumor maker response or duration on treatment for at least 16 weeks without progression), progression-free survival (PFS) and PFS at 6 months

Objective(s)	Endpoint(s)
To characterize the pharmacokinetic (PK) profile of RP-3500	Area under the concentration-time curve (AUC) from time 0 to last quantifiable concentration ($AUC_{0\text{-last}}$); AUC from time 0 to infinity (AUC_{inf}); AUC from time 0 to 8 hours ($AUC_{0\text{-}8}$); maximum observed plasma concentration (C_{max}); Dose normalized AUC and C_{max}; time to reach Cmax (T_{max}), terminal elimination half-life ($t_{1/2}$) and accumulation ratio (AR). Comparison of PK parameters after a single dose, multiple doses and between cycles
To assess PK parameters of RP-3500 monotherapy in fasted and fed states	Comparison of geometric mean ratios (GMR) and the 90% confidence intervals of $AUC_{0\text{-}8}$, $AUC_{0\text{-last}}$, AUC_{inf} and C_{max}
To assess the relationship between pharmacodynamic biomarkers and PK of RP-3500 in a subset of patents to aid in schedule decisions and assess the correlation with clinical outcomes	Pharmacodynamic biomarkers and PK concentrations and parameters
To evaluate the concordance between local and central methods for detecting ataxia telangiectasia-mutated and rad3-related inhibitor (ATRi) sensitizing biomarkers	Comparison of local results (NGS and IHC) and central results for ATRi sensitizing biomarkers by assessing number of patients positive or negative individual genes detected
To evaluate the impact of treatment with RP-3500 on QT/QTc interval	Absolute and change from baseline in QT/QTc interval determined from triplicate 12-lead ECGs (QTc corrected using both Bazett and Fridericia methods) and assessment of relationship to PK concentrations
[redacted]	
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted] mutations

3.2 Module 2 Objectives

Objective	Endpoint(s)
Primary	
To assess antitumor activity of RP-3500 when administered to eligible patients at the RP2D and schedule evaluated in the following arms: • ARM 1: ER+/HER2- breast, ampullary, pancreas, prostate, bile duct, and gastroesophageal junction tumors with likely pathogenic/pathogenic germline ATM mutations • ARM 2: leiomyosarcoma tumors with RNASEH2 loss or deleterious/likely deleterious BRCA2 mutations • ARM 3: tumors with other ATRi sensitizing biomarkers: ATRIP, CHTF8, FZR1, MRE11, NBN, RAD17, RAD50, RAD51B/C/D, REV3L, SETD2, and other genes agreed upon between the Sponsor and investigator	Objective response rate (ORR), overall response rate based on ORR and tumor marker response, duration of response (DOR), clinical benefit rate (CR, PR, tumor marker response or duration on treatment for at least 16 weeks without progression), progression-free survival (PFS), PFS at 6 months, and PSA response (for prostate cancer patients only)
Secondary	
To determine safety and tolerability of RP2D and schedule in the biomarker defined patient subsets	AEs, TEAEs, SAEs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, ECGs, and other assessments
To assess antitumor activity of RP-3500 in selected tumors with biallelic versus monoallelic alterations	ORR, overall response rate based on ORR and tumor marker response, duration of response (DOR), clinical benefit rate (CR, PR, tumor marker response or duration on treatment for at least 16 weeks without progression), PFS
To evaluate the preferred assay methods for defining how to select patients for ATRi sensitizing biomarkers for future studies	Comparison of different assay methods for detecting ATRi sensitizing biomarkers (NGS versus IHC)
To evaluate the concordance between local and central methods for detecting ATRi sensitizing biomarkers	Comparison of local results (NGS and IHC) and central results for ATRi sensitizing biomarkers by assessing number of patients positive or negative, individual genes detected
To further characterize the pharmacokinetic (PK) profile of RP-3500	PK concentrations and parameters for limited PK samples collected
[redacted]	
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Due to early discontinuation of enrollment in Module 2, the primary objective of this module will not be assessed. The data obtained from the 20 patients enrolled in Module 2 will be analyzed under the Module 1 objectives with patients in Module 1. This will enable a better evaluation of Module 1 objectives for monotherapy treatment.

3.3 Module 3 Objectives

Objective(s)	Endpoint(s)
Primary	
To assess the safety and tolerability of RP-3500 and talazoparib combination in eligible patients with advanced solid tumors	AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, ECGs, and other assessments
To define the MTD of RP-3500 and talazoparib combination and determine RP2D and schedule	DLTs Safety and tolerability (as described above)
Secondary	
To assess preliminary antitumor activity of RP-3500 and talazoparib combination in eligible patients with advanced solid tumors	Objective response rate (ORR), overall response rate based on ORR and tumor marker response, duration of response (DOR), clinical benefit rate (CR, PR, tumor marker response or duration on treatment at least 16 weeks without progression), and progression-free survival (PFS)
To assess PK of RP-3500 and talazoparib when administered in combination	Mean PK parameters of RP-3500 given in combination will be compared to the same mean PK parameters for patients who received an equivalent RP-3500 monotherapy dose
To determine the PK/pharmacodynamic relationships of RP-3500 and talazoparib combination to confirm dose/schedule	Population PK/pharmacodynamic modelling
To determine activity of RP-3500 and talazoparib combination in patients who progressed after RP-3500 alone	[redacted]
[redacted]	
[redacted]	[redacted]

[redacted]	[redacted]
	[redacted]

3.4 Module 4 Objectives

Objective	Endpoint(s)
Primary	
To assess the safety and tolerability of RP-3500 and gemcitabine combination in eligible patients with advanced solid tumors	AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, ECGs, and other assessments.
To define the MTD of RP-3500 and gemcitabine combination and determineRP2D and schedule	DLTs Safety and tolerability (as described above)
Secondary	
To assess preliminary anti-tumor activityof RP-3500 and gemcitabine combination in eligible patients with advanced solid tumors	Objective response rate (ORR), overall response rate based on ORR and tumor marker response, duration of response (DOR), clinical benefit rate (CR, PR, tumor marker response or duration on treatment for at least 16 weeks without progression), progression free survival (PFS)
To assess the PK of RP-3500 when administered in combination with gemcitabine	Mean PK parameters of RP-500 given in combination will be compared to the same mean PK parameters for patients who received an equivalent RP-3500 monotherapy dose
[redacted]	
[redacted]	[redacted]

3.5 Analysis Endpoints

The objective tables provide information on the study objectives and analysis endpoints per module split by primary, secondary and exploratory endpoints. The following section summarizes the primary and secondary analysis endpoints across the 4 different modules split by type of endpoint (safety, efficacy, PK and biomarker).

[redacted]

3.5.1 Safety Endpoints

- DLTs (Modules 1, 3, and 4)

- Incidence of treatment-emergent adverse events (TEAEs), treatment-related TEAE, TEAEs leading to death, serious adverse event (SAE), treatment-related SAE, TEAE leading to study drug discontinuation, TEAE leading to dose modifications summarized by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA) preferred term
- Number and percent of patients who need transfusion
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), Common Terminology Criteria for Adverse Events (CTCAE) graded laboratory toxicities, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, ECG parameters including QTc, physical exams (PEs), and usage of concomitant medications

3.5.2 Pharmacokinetic Endpoints

- PK concentrations of RP-3500 (and talazoparib for Module 3 only) for single and multiple dosing
- C_{max}, C_{max}/dose, $AUC_{(0-8)}$, $AUC_{(0-8)}$/dose, $AUC_{0\text{-last}}$, $AUC_{0\text{-last}}$/dose, AUC_{inf}, AUC_{inf}/dose, CL/F, Vz/F, accumulation ratio (AR) using AUC_{0-24}, T_{max} and $t_{½}$ for RP-3500 (talazoparib for Module 3 only) for single and multiple dosing

Note: The population PK/pharmacodynamic analyses will be developed and reported separately from the CSR and are out of scope for this SAP.

3.5.3 Efficacy Endpoints

Following is a list of efficacy endpoints. Further details on the derivation of endpoints can be found in Section 8.1.

- Overall response rate: defined as the proportion of patients with best response of CR or PR (confirmed or unconfirmed) according to RECIST v1.1 criteria based on investigator's assessment or confirmed cancer antigen 125 (CA-125) response by the Gynecological Cancer Intergroup (GCIG) criteria, or PSA response based on the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. For a tumor-marker responder, there must also be no evidence of radiologic or clinical progression prior to or within 4 weeks of the initial response
- Objective response rate (ORR): confirmed best overall response of CR or PR, based on investigator's assessment using RECIST v1.1 (Eisenhauer 2009). Analysis will be limited to patients with measurable disease
- Duration of response (DOR), based on investigator's assessment using RECIST v1.1. This endpoint is only applicable to patients with confirmed CR or PR based on RECIST v1.1
- Clinical benefit rate (CBR), based on achieving overall response or remaining on study treatment for at least 16 weeks without evidence of progression
- Progression-free survival (PFS) and rate of PFS at 6 months, based on investigator's assessment using RECIST v1.1
- Change in tumor size from baseline
- Tumor marker (CA-125 or PSA) response rate for evaluable patients with ovarian or prostate cancer

4 ANALYSIS POPULATIONS

4.1 DLT-Evaluable Population

The primary analysis population for dose decisions within Modules 1, 3, and 4 (dose finding cohorts) will be the DLT-evaluable population consisting of patients as described below:

- Patients who experience a DLT or
- Patients who receive at least 80% of planned total doses of RP-3500 during Cycle 1 (Module 1), both RP-3500 and talazoparib (Module 3), or 80% of RP-3500 and 100% of gemcitabine (Module 4), complete all required safety evaluations, and are observed through the end of Cycle 1

This population will be applied to dose escalation decisions in all these modules. Patients from Module 1c food effect will not be assessed for DLT and will not be included in the DLT-evaluable population.

DLT-evaluable population will only be applied to the summary of DLTs.

Module 2 patients will be combined with Module 1 patients for safety and efficacy analyses of patients treated with monotherapy. Module 2 patients were not evaluated for DLT.

4.2 Efficacy Population

Efficacy evaluable population includes all patients who received at least 1 dose of RP-3500, are evaluable for RECIST response or tumor marker response (GCIG criteria for CA-125 or PCWG3 criteria for PSA), and had at least 1 post-baseline radiographic tumor assessment or sufficient post-baseline tumor marker assessments meeting GCIG or PCWG3 PSA criteria, and without any key eligibility criteria deviation.

- Evaluable for RECIST response means patients are required to have measurable disease.
- Evaluable for tumor marker response applies to ovarian or prostate cancer patients only. Patients with ovarian cancer who had elevated baseline CA-125 levels (>70 kU/L) and two post-baseline CA-125 assessments at least 3 weeks apart will be considered CA-125 response evaluable. Patients with prostate cancer who had elevated baseline PSA (> 2 ng/mL) and two post-baseline PSA assessments at least 3 weeks apart will be considered as PSA response evaluable.

The primary efficacy population for monotherapy includes all Modules 1 and 2 patients who are part of the efficacy evaluable population and received at least 1 dose of RP-3500 above 100 mg/day. Dose level of >100 mg/day was predicted to achieve efficacious exposure based on preclinical data indicating that optimal antitumor activity was achieved at more than 6 hours of IC_{80} coverage with acceptable long-term tolerability. This definition represents a change to the current protocol, where patients at all dose levels are included.

The primary efficacy population for combination therapy (Modules 3 and 4, respectively) includes all patients who received at least 1 dose of RP-3500 and talazoparib (Module 3) or gemcitabine (Module 4), are evaluable for RECIST response or tumor marker response (GCIG criteria for CA-125 or PCWG3 criteria for PSA), and had at least 1 post-baseline radiographic

tumor assessment or sufficient post-baseline tumor marker assessments meeting CGIG or PCWG3 PSA criteria.

- Evaluable for RECIST response means patients are required to have measurable disease.
- Evaluable for tumor marker response applies to ovarian or prostate cancer patients only. Patients with ovarian cancer who had elevated baseline CA-125 levels (>70 kU/L) and two post-baseline CA-125 assessments at least 3 weeks apart will be considered CA-125 response evaluable. Patients with prostate cancer who had elevated baseline PSA (> 2 ng/mL) and two post-baseline PSA assessments at least 3 weeks apart will be considered as PSA response evaluable.

For efficacy analyses, patients will be presented based on initial dose assigned.

4.2.1 Safety Population

The Safety Population, used for the assessment of overall safety and tolerability, will consist of all patients who receive at least 1 dose of study drug. Patients will be presented based on initial dose assigned.

4.2.2 Pharmacokinetic Population

The PK Population will consist of all patients with at least 1 dose and any measurable RP-3500 (and talazoparib where applicable). The PK Population, used for the assessment of PK endpoints, will consist of all patients who have sufficient RP-3500 concentration data (and talazoparib where applicable) recorded to derive PK endpoints. For the PK Population, a dose modification, dose interruption, or missed dose will be presented with other individuals at the same starting dose but will be excluded from the corresponding descriptive statistics at subsequent cycles/days.

For all analysis populations, patients will be presented by the initial dose received.

5 DATA AND ANALYSIS CONSIDERATIONS

5.1 General Principles

All demography and safety data will be presented using the safety population, except the DLT reporting, which will be based on the DLT-evaluable population. Assessment of antitumor activity will be based on the Efficacy Population and PK data will be presented by the PK Population.

The majority of the analyses will be descriptive in nature. Unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, lower and upper quartile, minimum and maximum values) and the number and percentage of patients will be used for categorical variables. In general, missing data will be considered as missing and will not be imputed. Unless stated otherwise, percentages will be calculated out of the number of patients in the relevant analysis population.

Baseline will be the last assessment of the variable under consideration prior to the first dose of RP-3500.

In general, all data will be summarized by treatment regimens, dose level, or by module when appropriate.

Unless stated otherwise, safety and efficacy data will be presented descriptively by dose/schedule.

For Modules 1 (including Modules 1a, 1b, and 1c) and Module 1+2 combined, data will be summarized with following formats:

- Module 1-only patients: Data will be summarized by dose schedule (5 days on/2 days off [5/2] dosing schedule, 3 days on/4 days off [3/4] dosing schedule) and overall. Within each schedule, individual doses will be summarized, except the few patients treated ≤80 mg/day doses will be combined as ≤80 mg/day group
- Module 2-only patients: Data will be summarized together with Module 1 patients by dose level/schedule, except for patient disposition, demographics and baseline disease characteristics, where summaries will be provided by enrollment arm (1, 2, 3) as well
- Combined Module 1+2 (all monotherapy): Data will be summarized by dose schedule (5 days on/2 days off [5/2] dosing schedule, 3/4 dosing schedule) and overall. Within each schedule, the dose will be summarized by ≤100 mg/day versus >100 mg/day
- Combined Module 1+2 (all monotherapy): Data will also be summarized by potential RP2D dose levels: 120 mg once daily (QD; 3/4); 160 mg QD (3/4); and 160 mg QD (3/4), 2 weeks on/1 week off

Primary efficacy analysis for monotherapy in Module 1 and/or Module 2 will be performed on efficacy-evaluable patients who dosed at >100 mg/day.

Upon completion of the food-effect, PK-period evaluations, patients will continue on study following the dosing schedule of Module 1a (5/2) or Module 1b (3/4) at the highest evaluable dose level. If there is lack of food effect observed, patients in Module 1c will be combined with cohorts in Module 1a and Module 1b for the assessments of efficacy and safety analyses based on dose and dose schedule. No separate safety and preliminary efficacy analyses for Module 1c will be performed.

In addition, DLTs will be summarized by the initial individual dose levels, as well as the above grouping categories.

For Modules 3 and 4 (by arm), safety, efficacy and PK will generally be summarized by actual initial dose levels and schedule. Groupings may be considered (e.g., if multiple different dose level combinations and schedules are tested).

[redacted]

5.2 Study Day and Analysis Visit

5.2.1 Study Day

Study Day will be calculated from the reference start date (defined as the date of first dose of study drug), and will be used to show start/stop day of assessments/events:

- Study Day = (date of assessments/events - reference start date) if event/assessment is prior to the reference start
- Study Day = (date of assessments/events - reference start date + 1) if event/assessment is on or after the reference start

There is no Study Day 0.

5.2.2 Analysis Visit

Baseline value will be the latest non-missing result obtained prior to the start of RP-3500 dosing. The nominal visits will be used as analysis visits for the purpose of summarizing data over scheduled visits. No windowing algorithm will be used.

All recorded data will be included in the listings.

Vital signs assessment schedule varies across modules. Vital sign measurements will include blood pressure, heart rate, weight, temperature, and respiratory rate.

The following laboratory parameters will be reported in this study.

Hematology	Serum or Plasma Chemistry	Urinalysis	Circulating Tumor Marker
• White blood cell counts with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • Reticulocyte count	• Albumin • Alkaline phosphatase • ALT • AST • BUN or urea • Calcium • Chloride • Creatinine • Glucose • Lactate dehydrogenase • Phosphate • Potassium • Sodium • Total bilirubin • Total protein • Uric acid	• Specific gravity • Leukocyte esterase • Ketones • Protein • Glucose • Nitrite • Occult blood • Microscopy (if clinically indicated)	• PSA • CA-125 • CA15-3 • CA19-9 • CEA • CRP • CA2729AG • Beta Hc • Human epidermal growth factor receptor 2

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.

5.3 Handling of Missing Data

There will be no imputation of incomplete or missing data other than the dates mentioned below. In general, imputation should only be applied if needed for the analyses.

5.3.1 Date Imputation Rules

The following date imputation will be applied when needed for derivation of the study day or other analysis variables. However, the original date information will be presented in the data listings.

Initial diagnosis date or other historical dates related to diagnosis/prior treatment (as applicable):

- If year is missing, do not impute
- If only day is missing, impute day as 15th of the month
- If day and month are missing, impute as July 1 of the year
- Note, if the first dose date of study drug is before above imputed date, impute the diagnosis date as the date before the first dose date since diagnosis is expected to be confirmed before the study

Concomitant medication start date:

- If year is missing (or completely missing), do not impute
- If (year is present and month and day are missing) or (year and day are present and month is

missing), impute as January 1

- If year and month are present and day is missing, impute day as first day of the month

Concomitant medication end date:

- If year is missing (or completely missing), do not impute
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31
- If year and month are present and day is missing, impute day as last day of the month
- If the imputed end date is earlier than the observed/imputed medication start date, the end date will be imputed as the same as the start date

Poststudy therapy/radiotherapy start date:

- If year is missing (or completely missing), do not impute
- If year is present and month and day are missing:
- If year is the same as the year of last dose date, impute as the last dose date + 1
- If year is greater than the year of last dose date, impute as January 1
- If year and day are present and month is missing:
- If year is the same as the year of last dose date, and day is not greater than the day of last dose date, impute the month as the month of last dose date + 1
- If year or day is greater than the year or day of last dose date, impute the month as the month of last dose date
- If year and month are present and day is missing:
- If year and month are the same as the year and month of last dose date, impute as first last dose date + 1
- If year or month is greater than the year or month of last dose date, impute day as first day of the month

Poststudy therapy/radiotherapy end date:

- If year is missing (or completely missing), do not impute
- If (year is present and month and day are missing) or (year and day are present and month is missing, impute as December 31
- If year and month are present and day is missing, impute day as last day of the month
- If the imputed end date is earlier than the observed/imputed poststudy therapy/radiotherapy start date, the end date will be imputed as the same as the start date

Missing dates in AEs (only applicable in analysis stage when complete dates are required, not for the purpose of data listing).

Start dates of AEs will be imputed as follows:

- Completely missing start date will be imputed as the date of first dose
- Start date missing both month and day will be imputed as:
    - Date of first dose if the year of the start date is the same as the date of first dose
    - Otherwise, January 1 of the year of the start date will be used
- Start date missing day will be imputed as:
    - Date of first dose if the year and month of the start date are the same as the date of first dose
    - Otherwise, the first of the month of the start date will be used

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead.

5.3.2 Relationship and Severity Imputation Rules for Adverse Events

Missing relationship will be considered as 'Related' if the AE started on or after the date of first dose. Missing severity will not be imputed. All AEs are expected to have non-missing severity (to toxicity grade) at the time of database lock.

6 DISPOSITION, DEVIATIONS AND PATIENT CHARACTERISTIC DATA

An overall patient disposition summary will be presented for all patients to show the number of unique patients who entered the study.

In addition, patient disposition will be presented by module and by dose/schedule with percentages based on the safety population. The following information will be presented for disposition:

- Patients treated
- Included in each analysis population (DLT evaluation, safety, PK and Efficacy)
- Ongoing/discontinued study treatment at the data cut-off
- Including reasons for discontinuation of treatment as per the electronic case report form (eCRF)

[redacted]

- Ongoing/withdrawn/completion from study at the data cut-off
- Including reasons for study termination as per the eCRF

[redacted]

Disposition data will be listed for all patients and will include patient status, date of discontinuation from treatment, date of withdrawal from study and reason for treatment discontinuation and study withdrawal. In addition, the number and percentage of patients by country will be summarized.

6.1 Protocol Deviations

Protocol deviations are identified by clinical research associates, monitors, or other team members per Protocol Deviation Management Plan and Protocol Deviation Guidance. Protocol deviations are documented within the Clinical Trial Management System. Protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of study data or that are determined to have affected patients' rights, safety, or well-being are classified as important protocol deviations. After finalization, protocol deviation data will be imported into SDTM and ADaM datasets.

There is no per protocol analysis population defined for this study; therefore, patients will not be excluded from the data analysis and reporting based on deviations.

Following review of all reported deviations and associated data and prior to database lock, other important deviation categories may be added. Only important deviations will be listed and summarized. Other deviations considered not important (out of window assessments, etc.) will not be listed but will be available within the SDTM and ADaM DV dataset.

6.2 Demographic and Baseline Characteristics

Demographics will be summarized by module and dose schedule for the safety population. Baseline demographic will include age at informed consent, age group (<65 years and ≥65 years), gender, race, ethnicity, height (cm), weight (kg), body mass index (kg/m^2). Baseline characteristics will include primary tumor type and ECOG performance status.

6.3 Genotype and mutation Status at Enrollment

The following data on the mutation status of patients at enrollment will be listed and summarized for monotherapy (Modules 1, 2), and for combinations regimens (Module 3 and Module 4), respectively:

- Mutations/genes detected based on local tests

A patient may test positive for more than 1 enrollment gene and will be summarized under the primary gene curated by central review. Additional subsets will also be presented such as primary tumor type.

If additional local baseline genomic data with more informative genotypic information with supportive documentation becomes available during the course of the study, the updated genotype information will be used for analyses purposes.

6.4 Disease Characteristics

The following disease characteristics will be summarized based on the Safety Population:

Disease history:

- Time since initial diagnosis (in months)
- Time since presentation of metastatic disease
- Primary tumor type
- Histology and grade of disease at diagnosis

Prior anticancer therapy:

- Number of lines of systematic therapy for cancer treatment prior to study entry: the line of therapy is currently not recorded directly in the database. This information will be provided outside of the database through Sponsor clinical/medical review of all reported prior treatment regimens for patients and provide the information in xls format to be incorporated into SDTM. More details will be provided in ADaM specification and reviewer guide
- Prior use of platinum-based regimen
- Prior use of poly ADP ribose polymerase inhibitor
- Prior use of PD-1/L1 regimen
- Prior use of gemcitabine (Module 4 patients only)
- Information on last anti-cancer treatment regimen, if applicable:
    - Best response
    - Disease progression (yes, no)
    - Time since end of last treatment in months
    - Duration of last treatment

- Reason for end of regimen

6.5 Medical History

Medical history will be coded using the latest version of MedDRA and will be summarized for the Safety Population, using SOC and preferred term (PT). The table will include the number and percentage of patients and will be sorted in alphabetical order by SOC and PT. A patient will only be counted once within a class. A listing of medical and surgical history will also be provided.

6.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients will be tabulated by WHO drug generic term for the Safety Population.

Prior medications will include medications which started prior to the date of the first dose of study treatment. A summary table will present the numbers and percentages of patients who received prior therapy, including prior systemic anticancer therapy, prior radiation, prior surgery, and best response to the prior therapy, if known. Concomitant medications will include medications which started or were ongoing at the date of first dose of study treatment through to 30 days after the last dose of study treatment, or to the start of subsequent anticancer therapy, whichever occurs first.

Details of prohibited concomitant medications are provided in the protocol. In order to programmatically determine prohibited medications, a coded list of all prohibited medications will be available prior to database lock. Listings of prior and concomitant medications will display a flag for prohibited medications. This information will be used to identify protocol deviations.

7 SAFETY AND EXPOSURE DATA

Safety and tolerability will be assessed in terms of AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, and ECGs including QTc.

Toxicity will be assessed using the NCI CTCAE version 5.0 (v5.0) unless otherwise specified. A toxicity will be considered dose limiting if it occurs during the first treatment cycle, is deemed to be related to treatment and it meets the DLT criteria as defined in the study protocol. DLTs will be evaluated during the study to determine dose levels for Modules 1, 3, and 4. DLTs will be listed and summarized based on the DLT-Evaluable Population by module and initial dose received.

DLTs will be identified from the AE eCRF where the AE is selected as a DLT. All AEs reported as DLTs on the eCRF will be included even if they were not considered DLTs by the SRC during the study reviews.

The maximum tolerated dose (MTD) will be defined as the highest dose with a DLT rate <30% when the DLT rate is monotonic (or nondecreasing) as dose increase. Simulations confirm that with this study design, defining the MTD this way is equivalent to using an isotonic regression with a descending pooled adjacent violators algorithm, which isthe recommended method in the publication for Bayesian Optimal Interval study designs (Yuan 2016).

7.1 Adverse Events

AEs will be coded using MedDRA version 24.0 and graded according to NCI CTCAE v5.0. All laboratory test results will be classified for toxicity grade according to the NCI CTCAE v5.0

criteria.

Treatment-emergent adverse events (TEAEs) are those events that occur or worsen on or after the first dose of study drug up through 30 days post the last dose (or cross over to a different module) or the start of subsequent anticancer therapy. Treatment-related SAEs are included in TEAEs and reported indefinitely. AEs are considered related to treatment if the relationship to RP-3500-01 or the other combination drug (in the study regimen) is "Related" (include unknown relationship) as indicated on the AE eCRF page.

An overview summary table of the number and percentage of patients in each of the categories listed below will be presented. This summary will be presented based on all patients in the study (overall summary to summarize unique patients) and then repeated split by module and dose/schedule (see Section 5.1 for general presentation format).

- All TEAEs
- Treatment-related TEAEs
- DLTs
- TEAEs with NCI CTCAE grade ≥3
- Treatment-related TEAEs with NCI CTCAE grade ≥3
- Serious TEAEs
- Treatment-related serious TEAEs
- TEAEs with outcome of death
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose modification (i.e., dose reduced, or dose interrupted) of study treatment

Note that treatment-related AE is defined as having relationship of related or unknown relationship to any of the study drugs in the regimen, not just related to RP-3500, unless otherwise specified.

TEAEs will be further summarized by SOC, PT, and by NCI CTCAE toxicity grade (where applicable). For summary tables, an AE that occurs more than once within a SOC and PT will be counted only once using the worst NCI toxicity grade experienced.

AEs of special interest may be defined during the study based on emerging clinical data and will be listed and summarized by NCI CTCAE v5.0.

Data listing will be provided for all TEAEs and serious TEAEs.

An AE table of most frequently occurring TEAEs, showing all events in at least 5% of patients across all modules, will be summarized by PT, by decreasing frequency based on all patients. This cutoff may be modified after reviewing the data. TEAEs with outcome of death, leading to dose reduction, dose interruption or discontinuation of study treatment will be summarized by PT. Corresponding listings will be provided. If the number of occurrences is low (e.g., when ≤ 5 patients involved), only listings will be provided.

For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group for summarizing. Any AE occurring before the first dose of study treatment will be included in the data listings but will not be included in the AE summary tables. Summary tables will include only TEAEs. AEs occurring after the 30-day follow-up period after discontinuation of study treatment will be listed but will not be included in the summaries.

The number of patients that received transfusions, reason for transfusion, and type of transfusion will also be summarized by dose groups for each module. A separate list will be provided for transfusion.

For Module 1c patients (food effect):

- Any AE with a start date after daily dosing commences will be reported under the relevant Module 1a or Module 1b dose and schedule
- Any AEs with a start date prior to commencement of daily dosing will be considered as part of the food effect evaluation under the dose received. These AEs will be summarized separately. A summary table may be replaced by a listing if <5 total AEs reported

[redacted]

All crossover patients should be flagged in the original module listing.

A listing of all deaths and causes of deaths will be provided.

7.2 Treatment Exposure

Exposure will be derived for RP-3500, talazoparib (for Module 3 only) and gemcitabine (for Module 4 only).

Duration of exposure will be defined as the duration between the first and last dose of study drug:

- Duration of exposure = last dose date - first dose date + 1

Module 1c patients received a single dose during the food effect PK Period on Day -3 with a break for 2 days and then started their daily dose. Their maximum possible dose and total dose received will be calculated from the start of their daily dose then add the single dose received during the PK Period.

The last dose date will be obtained from the end-of-treatment (EOT) eCRF page. For combination regimen, last dose date will be the later of the 2 drugs' last dose date from the EOT page. [redacted]

Number of days dosed will be derived as the number of days a patient received a dose of treatment (i.e., excludes off treatment days and any missed doses).

Total dose received (mg) is the total dose the patient received during their time on treatment:

- Total dose received = Number of days dosed × dose received

Dose received for gemcitabine will be summarized by number of infusions received during the study period.

If a patient had a dose reduction/change during treatment, then the total dose received will be calculated for each actual dose received and then summed to give the total dose received.

Total dose received:

$$\sum_{i=1}^{k} (number\ of\ days\ dosed\ at\ dose\ xi * dose\ xi)$$

for i=1 to k where i represents the number of dose levels received and k= number of distinct dose levels

Maximum expected dose will be derived as the maximum dose a patient could have received without any interruptions or reductions based on the time period between the date of first dose and date of last dose after excluding days when dosing information is not available, accounting for the number of treatment days per week. This is assuming the days without dosing information is missing at random.

Dose intensity will be derived as:

Dose intensity = (total dose received/maximum possible dose) × 100%

A dose interruption will be defined as a planned interruption where a decision is made to interrupt the dose temporarily. Dose interruptions will be captured on the eCRF.

A dose reduction is any reduction in dose/schedule compared to the initial dose.

Patients who do not have an end of treatment date in the eCRF at the time of analysis and reporting will be considered ongoing treatment. For deriving exposure, ongoing patients will be assumed to be ongoing at the date of the data cut off (DCO); therefore, the DCO date will be used to derive exposure. For when the EOT date is available, but the last dose date is missing on the EOT eCRF, the last dose date will be imputed by the end of treatment date.

Exposure will be listed and summarized by the Safety Population and presented by module and dose/schedule.

The following will be presented for RP-3500, talazoparib (Module 3 only) and gemcitabine (Module 4 only):

- Duration of exposure (days)
- Number and percent of patients with at least 1 cycle, with at least 2 cycles, etc
- Number of cycles treated (completed)
- Total dose received (mg)
- Dose intensity (%)
- Number and percent of patients with at least 1 dose interruption reported in dosing log
- Further broken down by number with 1, 2 or ≥3 interruptions
- Number and percent of patients with dose interruption in Cycles 1, 2, or ≥3
- Number and percent of patients with at least 1 dose interruption reported in dosing log by considering only those incidences when AE is indicated as a reason
- Further broken down by number with 1, 2 or ≥3 interruptions
- Number and percent of patients with dose interruption in Cycles 1, 2 or ≥3
- Number and percent of patients with at least 1 dose reduction reported in dosing log
- Further broken down by number with 1, 2 or ≥3 reductions
- Number and percent of patients with dose reduction in Cycles 1, 2 or ≥3

- Number and percent of patients with at least 1 dose reduction reported in dosing log considering only those incidences when AE is indicated as a reason
- Further broken down by number with 1, 2 or ≥3 reductions
- Number and percent of patients with dose reduction in Cycles 1, 2 or ≥3
- Number of patients with any dose escalation per protocol

Patients with both an interruption and reduction will be included in both the interruption and reduction summaries.

7.3 Laboratory Evaluations

All laboratory data recorded in the eCRF will be listed. Out-of-reference range values will be flagged as high or low in the listings. Laboratory values will be converted into results in Système International (SI) units according to the National Institute of Science and Technology in the SDTM datasets. The results in SI units will be used in the summary tables.

Box plots for mean changes from baseline over time for laboratory parameters will be produced by module and dose/schedule based on the Safety Population and the number of patients with data at the relevant timepoints.

Selected hematology assessments (hemoglobin, neutrophils, and platelets) will be also presented in shift tables showing baseline grade versus maximum grade on study for laboratory assessment with NCI CTCAE grading, based all postbaseline data including unscheduled assessments. The denominator for each on-treatment maximum grade is the total number of patients in the corresponding row for baseline grade (i.e., the baseline row totals). The shift from baseline to worst value as well as last value during the treatment period (up to last dose date for last value) will be summarized.

If worst criteria could be a low or a high value or an increase or decrease (i.e., in both directions) then shift tables should be split to show shift from baseline to worst low/decrease value and then repeated for worst high/increase value. For example, NCI CTCAE grade criteria is given for both lymphocyte count increased and lymphocyte count decreased.

Postbaseline liver function tests including unscheduled assessments will be summarized in the following categories in Safety Population. A listing of patients whose laboratory values meet Hy's Law criteria will also be provided.

- Aspartate aminotransferase >3 × upper limit of normal (ULN) or 3 × Baseline (if baseline value is >ULN)
- Alanine aminotransferase >3 × ULN or 3 × Baseline (if baseline value is >ULN)
- Alkaline phosphatase >3 × ULN or 3 × Baseline (if baseline value is >ULN)
- Total bilirubin >2 × ULN

7.4 Vital Signs and Abnormalities

Descriptive statistics of pulse/heart rate, blood pressure (systolic and diastolic) (supine/semi-recumbent), weight, and body temperature values will be summarized at baseline and post baseline visits, and changes from baseline will be summarized for post baseline visits based on the Safety Population. A separate listing will include all the vital sign measurements, including those from the unscheduled visits.

The following postbaseline vital signs will be summarized based on the Safety Population:

- Maximum postbaseline in systolic blood pressure:
    - No increase

  - Increase <20 mmHg
  - Increase ≥20 mmHg
    - ≥160 mmHg and increase ≥20 mmHg
- Maximum postbaseline in diastolic blood pressure:
  - No increase
  - Increase <20 mmHg
  - Increase ≥20 mmHg
    - ≥100 mmHg and increase ≥20 mmHg

For the number of patients meeting each category for the postbaseline results or for the change from baseline, the numerator is the number of patients with meeting the criterion at any postbaseline including the unscheduled and the denominator is the number of patients with normal baseline and at least 1 postbaseline assessment including unscheduled visits in the Safety Population.

A listing for patients with any postbaseline potentially clinically significant changes listed above will also be presented.

Box plots for changes from baseline over time will be produced by module and dose/schedule based on the Safety Population and the number of patients with data at the relevant timepoints. Timepoints where there are <3 observations at dose/schedules will not be presented.

7.5 12-lead ECG

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) of ECG parameters, including PR interval, respiratory rate interval, QRS duration, and QTcF interval (Fridericia's corrections) will be presented for baseline, each postbaseline visit, and change from baseline to each postbaseline visit for Safety Population. All measurements, including those during unscheduled visits, will be provided in data listings. The average of triplicate 12-lead ECG results will be used for descriptive statistics.

Overall ECG investigator interpretation category (normal, abnormal not clinically significant), abnormal clinically significant, and not evaluable) is collected in the eCRF at baseline and each scheduled postbaseline visit. Shifts in ECG interpretation at baseline to worst postbaseline, as well as last value during the treatment period (up to last dose date for last value) will be presented. For triplicate 12-lead ECG results with numerical value collected at a visit, the average of triplicate 12-lead ECG results will be used as the interpretation at baseline as well as postbaseline.

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 patients meeting each category for the postbaseline results, the numerator is the number of patients meeting the criterion at any postbaseline including unscheduled visits and

the denominator is the number of patients with baseline and at least 1 postbaseline assessment including unscheduled visits in the Safety Population.

Box plots for absolute and change from baseline for QTcF will be produced by module and split by dose/schedule based on the Safety Population and the number of patients with data at the relevant timepoints. All ECG parameters will be listed in a data listing. All ECG tables and listings will be reported on the safety analysis set.

7.6 Physical Examination and ECOG

PE results for patients with abnormalities identified from PE will be listed.

Shift tables of baseline ECOG performance to worst postbaseline status will be summarized as the number and percent of patients in each ECOG category based on the Safety Population.

Any change in PE findings assessed as clinically significant should be recorded as an AE or SAE.

8 EFFICACY DATA

8.1 Derivation of Efficacy Endpoints

8.1.1 Overall Response Rate

Overall response rate is defined as the proportion of patients with best response of confirmed CR or PR (i.e., 2 visit responses of either CR or PR at least 4 weeks apart) or unconfirmed CR or PR according to RECIST v1.1 (Appendix 1), or confirmed CA-125 response by GCIG criteria (Appendix 2), or PSA response based on PCWG3 (Appendix 3) among efficacy evaluable patients. For a tumor-marker responder, there must also be no evidence of radiologic or clinical progression prior to or within 4 weeks of the initial response.

Specifically, PSA response is defined as having ≥50% reduction from baseline in PSA, confirmed at the next assessment of at least 3 weeks later. Only those patients with prostate cancer and baseline PSA value ≥2 ng/mL prior to treatment will be considered evaluable for PSA response.

CA-125 response is defined as having ≥50% reduction from baseline, confirmed at the next assessment of at least 3 weeks later. Only those patients with ovarian cancer and baseline CA-125 >2 times ULN (reference range is 0-35 kU/L) will be considered evaluable for CA-125 response.

8.1.2 Objective Response Rate

ORR is defined as the proportion of patients with a confirmed response of CR or PR (i.e., 2 visit responses of either CR or PR at least 4 weeks apart with no intervening PD) according to RECIST v1.1 criteria among efficacy-evaluable patients with measurable disease.

Response will be assessed based on all evaluable assessments up to and including progression per RECIST v1.1. Responses occurring following subsequent anticancer therapy will be excluded from the assessment of ORR but will be included in the listing.

8.1.3 Duration of Response

DOR will be derived for patients with a confirmed CR or PR only. DOR is defined as the time from the date of the earliest qualifying response (CR or PR) and the date of disease progression or death for any cause, whichever occurs earlier, based on RECIST v1.1. Note, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

Given responses are required to be confirmed, the date of earliest qualifying response is the latest date for the visit where the initial overall visit assessment of CR/PR was observed rather than the confirmation visit assessment.

For patients who are alive without disease progression following response, DOR will be censored on the date of the last evaluable tumor assessment or date of data cut-off whichever comes first.

8.1.4 Clinical Benefit Rate

CBR is defined as having a confirmed or unconfirmed CR or PR after the first dose of RP-3500 according to RECIST v1.1, confirmed CA-125 by GCIG criteria, or PSA response based on PCWG3, or remain on study treatment for at least 16 weeks without evidence of progression.

Specific definition for CA-125 response and PSA response is provided in Section 8.1.1. For a tumor-marker responder, there must also be no evidence of radiologic or clinical progression prior to or within 4 weeks of the initial response.

8.1.5 Change in Tumor Size

The best percent change in target lesion (TL) size compared to baseline will be derived for each visit as:

- Percent change in TL at Visit X = [(Visit X TL sum of diameters – Baseline TL sum of diameters)/Baseline TL sum of diameters] *100

The best percent change will be derived as the largest decrease or smallest increase (in the absence of a decrease) up to and including progression or last evaluable assessment in the absence of progression. If a patient receives another anticancer therapy prior to progression, then data up until the last evaluable TL assessment prior to the start of subsequent therapy will be included.

The sum of diameters should be a sum of all target lesions identified at the baseline.

8.1.6 Progression-Free Survival

PFS is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by RECIST v1.1 criteria or death from any cause. For patients with prostate cancer in Module 2, progression can also be determined by bone lesions (PCWG3).

TL, NTL and new lesion assessments may be performed on different dates. The following rules will be applied for determine progression and censoring dates:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression. For example, if progression was due to a new lesion only then the date of the new lesions would be used. If progression was due to TLs and a new lesion, then the earliest of the TL and new lesion dates would be used
- Patients who are alive and free from disease progression will be censored at the date oftheir last evaluable tumor assessment prior to or equal to the data cut-off date
- Any patient who dies in the absence of progression after 2 or more missed assessments will be censored at the date of their last radiographic tumor assessment. Specifically, if the death date is >12 weeks from the last tumor assessment, the death date will not be used for the calculation of PFS
- If a patient has no baseline tumor assessment/no post dose tumor assessments then they will be censored at 0 days for PFS, unless they died within 12 weeks from the date of first dose (and also before cut-off), in which case their death date will be used as a PFS event

The rules of defining censoring/event for PFS are in Table 3.

Table 3 Censoring Rule for Time-to-Event Analyses (PFS) Based on Radiographical Tumor Assessment or Death

Situation	Date of Censoring or Date of Event	Censor
Documented PD before data cutoff	Date of first PD	0 (observed)
No PD, but death date is within **12** weeks from the last adequate postbaseline assessment[a]	Date of death	0
No PD, no postbaseline assessment, and death date is within 12 weeks from the date of first dose	Date of death	0
No PD, no postbaseline assessment[a], and death date >**12** weeks from the date of first dose	Date of the first dose	1
No PD, no postbaseline assessment[a], and no death	Date of the first dose	1
No PD, death date >12 weeks from the last adequate postbaseline assessment[a] (e.g., 2 or more consecutive missed scheduled disease status assessments and the gap >**12** weeks)	Date of last adequate tumor assessment[a]	1
No PD or death, but with last adequate assessment[a] before data cutoff	Date of last adequate tumor assessment[a]	1

PD = progressive disease.

a. Adequate disease assessment is defined as a response assessment other than "not assessed" or "not evaluable."

This Censoring Rule is used for the data after implementation of data cut off.

PFS at 6 months will be reported based on Kaplan-Meier (KM) methods as the number and percent of patients estimated to be progression free at 6 months.

8.1.7 PSA Response Rate

This is only for patients with prostate cancer with elevated baseline PSA level in Module 1 and Module 1 and Module 2 combined.

PSA response rate is defined as having ≥50% reduction from baseline in PSA, confirmed at the next assessment. Only those patients with baseline PSA value ≥2 ng/mL prior to treatment will be considered for denominator of this endpoint.

8.2 Efficacy Analysis Methods

For overall response rate, ORR, CBR, and PSA response rate, the number and percentage of patients along with an exact binomial 95% confidence interval (CI), using the Clopper-Pearson method, will be presented.

In addition, a summary of the best objective response will be presented which will include the number and percentage of patients with a best response of CR, PR, stable disease (SD), PD, and not evaluable.

In general, time-to-event endpoints (DOR, PFS, and time to PSA progression) will be analyzed using the KM method and results will be summarized by the 25th, 50th, and 75th percentiles, if estimable, with associated 2-sided 95% CIs. KM plots will be provided. For PFS, the number (%) of patients with an event and the number (%) of patients censored will also be presented. The rate of PFS at 6 months will be derived from the corresponding KM curves and the associated 95% CIs calculated using Greenwood's formula on the ln[-ln(survival scale)] and back transformed.

Maximum reduction in tumor size will be summarized by n, mean, standard deviation, median, 25th quartile and 75th quartile, minimum, and maximum. The spider plots displaying change in tumor size over time for each patient will also be provided for each module and dose/schedule group.

In addition, waterfall plots showing the best percentage change from baseline (largest decrease or smallest increase in the absence of a decrease) in the sum of the TL sizes will be produced for each module by dose/schedule group indicating the best objective response for each patient.

Swimmer plots will be produced for each module and dose/schedule group/arm to show the duration of study treatment per patient with indicators for date of response, progression, and date of death, where applicable. Include information on tumor type and genotype for each patient.

Efficacy summaries will be based on efficacy-evaluable population and primary efficacy population as defined for the corresponding module, unless otherwise specified.

8.2.1 Monotherapy: Module 1 and Module 2 Combined

Given the early termination of Module 2 and limited number of patients enrolled in this module, Module 1 and Module 2 patients will be combined for monotherapy efficacy evaluations.

To address the protocol specified Module 1 and Module 2 secondary objective of preliminary assessment of antitumor activity, the above efficacy summaries will be presented based on the efficacy population of Module 1 and Module 2 combined.

Based on PK and pharmacodynamic analyses, it was determined that plasma exposures at doses >100 mg/day of RP-3500 achieved predicted efficacious exposures with target and pathway modulation, and thus were potentially biologically effective dose levels in patients. The antitumor activity at doses >100 mg/day of RP-3500 are thus reported separately for efficacy endpoints as primary.

The following subgroup analysis will be performed where there are enough patients (i.e., ≥5 patients in each category):

- By tumor type and tissue origin such as ovarian, prostate, pancreas, breast, colorectal, sarcoma, bile duct, and other
- By genotype such as ATM, BRCA1, BRCA2, SETD2, CDK12, RAD51B/C, and other
- By the allelic status of the eligibility gene (i.e., biallelic loss of function (Biallelic, Suspected Biallelic) versus nonbiallelic loss of function (Monoallelic, CHIP, No Loss, Subclonal) versus Unknown (Indeterminate, Inconsistent, Not Tested/NA)

8.2.2 Module 3

Module 3 addresses the secondary objectives of:

- Preliminary assessment of antitumor activity for RP-3500 in combination with talazoparib
- To determine activity of RP-3500 in combination with talazoparib in patients who previously progressed on RP-3500 monotherapy

The above efficacy summaries will be presented split by Module 3a (excludes crossover patients) [redacted] based on the primary efficacy population and by dose levels.

To explore the efficacy within subgroups of interest, data from Module 3 may be presented in the following subgroups:

- By tumor type such as ovarian, breast, prostate, and pancreas
- By genotype such as ATM, BRCA1, and BRCA2

8.2.3 Module 4

Module 4 addresses the secondary objectives of:

- Assessing preliminary antitumor activity of RP-3500 in combination with gemcitabine
- Assessing the PK of RP-3500 in combination with gemcitabine

The above efficacy summaries will be presented based on the primary efficacy population by arm and initial dose levels and schedule.

To explore the efficacy within subgroups of interest, data from Module 4 may be presented in the following subgroups:

- By tumor type such as ovarian, breast, prostate, and pancreas
- By gynecological and non-gynecological malignancies
- By genotype such as ATM, BRCA1, and BRCA2

The PK profile of RP-3500 will be presented based on the PK population. The PK of gemcitabine will not be assessed as part of this study.

9 PHARMACOKINETIC PARAMETERS DATA

All PK data will be presented based on the PK Population and presented by module and dose/schedule. PK data may be pooled for patients receiving the same dose/schedule in Module 1 and Module 2, but this will be confirmed prior to analysis depending on the similarity of PK sampling across the modules and the number of patients.

PK concentrations and parameters will be listed for all patients in the PK Population. Individual patient and mean plasma RP-3500 concentration-time profiles will be plotted for each module and dose/schedule. For Module 3, the same plots will be produced for talazoparib.

The following summary statistics will be presented for C_{max}, C_{max}/dose, $AUC_{0\text{-}24}$, $AUC_{0\text{-}24}$/dose, $AUC_{(0\text{-}8)}$, $AUC_{(0\text{-}8)}$/dose, $AUC_{0\text{-}last}$, $AUC_{0\text{-}last}$/dose, AUC_{inf}, AUC_{inf}/dose, CL/F, Vz/F and AR, for RP-3500 and talazoparib on the respective cycles and days appropriate to a given module and schedule:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)

- Coefficient of variation (CV [calculated as CV =100*standard deviation/mean], where s is the standard deviation of the untransformed data)
- Geometric coefficient of variation (geom CV) calculated using log transformed data
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations (n)

T_{max} will be summarized as median, minimum, maximum and number of observations (n) nonquantifiable (NQ) values of plasma concentrations will be handled as follows:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean, CV, geom CV, arithmetic mean and standard deviation will be calculated by substituting the limit of quantification for values which are NQ
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, geom CV, arithmetic mean, and standard deviation will be reported as not calculable
- If all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV, geom CV and standard deviation as not calculable

For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual patient plots by time, the actual PK sampling time will be used.

Given that no formal hypothesis testing is being undertaken for this module, no statistical inference will be made.

9.1 Relationship between Pharmacokinetic and Dose

The relationship between the parameters C_{max}, AUC_{inf}, $AUC_{0\text{-}last}$ and dose will be examined using the power model on C1D1 and either Cycle 1 Day 3 or Day 5, depending on schedule, i.e.,

- $P = a \times Dose^b$

where P represents the parameter and a and b are constants. A value of b of approximately 1 indicated linear PK.

The following model will be fitted:

- Ln (PK parameter) = intercept + b*ln (dose)

From this model, the 90% CI for the slope (which represents b) will be derived and if the CI contains the value 1 then the PK data will be considered consistent with dose proportionality.

Dose proportionality will be assessed within a schedule including all doses across a schedule, regardless of module.

9.2 Pharmacokinetic Analysis for Food Effect (Module 1c Only)

Patients in Module 1c receive a single dose of RP-3500 in the fed state on Day -3, followed by a single dose of RP-3500 in the fasted state on Day 1.

The following model will be used to estimate the effect of food based on the patients enrolledin Module 1c:

- Natural-log-transformed AUC_{inf} (if data permit), $AUC_{0\text{-last}}$ and C_{max} for RP-3500 will be analyzed using a mixed effect model with treatment (fed versus fasted) as fixed effects and patient as a random effect

Estimates of the adjusted mean differences (test/reference) and corresponding 90% CI will be obtained. The adjusted mean differences and 90% CI for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CI for the ratios. RP-3500 in the fasted state will be considered the reference treatment.

The 90% CIs will be examined to determine if they are within limits of 80% to 125% for the different parameters. Additional analyses of AUC_{inf} (if data permit), $AUC_{0\text{-last}}$ and C_{max} may be provided if outliers are identified.

9.3 Effect of Talazoparib on RP-3500 (Module 3 Only)

The effect of talazoparib on the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} of RP-3500 will be evaluated in patients from Module 3.

PK parameters for RP-3500 and talazoparib will be calculated using noncompartmental analysis and summarized as described above.

The mean $AUC_{0\text{-last}}$ and AUC_{inf} and C_{max} of RP-3500, when co-administered with talazoparib, will be compared side by side with the mean $AUC_{0\text{-last}}$ and AUC_{inf} and C_{max} parameters from patients that received RP-3500 monotherapy at an equivalent dose and dosing regimen from Module 1.

9.4 Effect of Gemcitabine on RP-3500 (Module 4 Only)

The effect of gemcitabine on the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} of RP-3500 will be evaluated in patients from Module 4.

PK parameters for RP-3500 will be calculated using noncompartmental analysis and summarized as described above.

The mean $AUC_{0\text{-last}}$ and AUC_{inf} and C_{max} of RP-3500, when co-administered with gemcitabine, will be compared side by side with the mean $AUC_{0\text{-last}}$ and AUC_{inf} and C_{max} parameters from patients that received RP-3500 monotherapy at an equivalent dose and dosing regimen from Module 1.

9.5 Relationship Between Pharmacokinetic Concentrations and QTc

To assess the relationship between drug exposure and QTc, a plot of change from baseline in QTc (for Fridericia's corrections) versus PK concentrations for RP-3500, at the same timepoints, will be presented.

The plot will include data pooled across all doses, schedules, and modules.

Further statistical models may be fitted to explore any relationship further with data from Module 3 adjusted for talazoparib PK concentrations. Any additional analyses will be conducted as part of the population PK/pharmacodynamic modelling work which is out of scope for this SAP (Section 9.6).

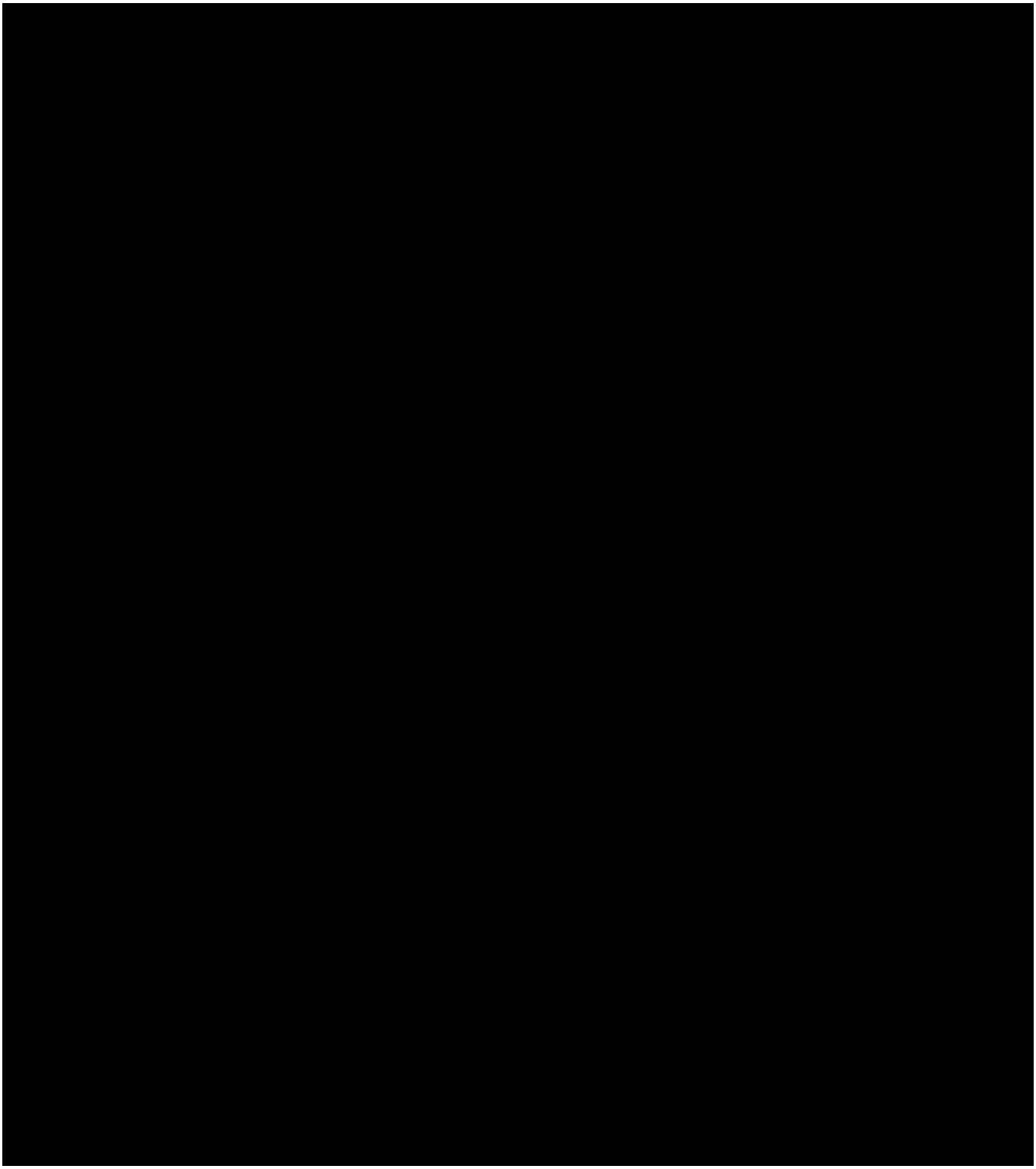
9.6 Population Pharmacokinetic/Pharmacodynamic Modeling

Population PK modelling will be performed on the RP-3500 concentration-time data collected from this study to quantitatively describe the PK, explore the PK variability, and identify any covariate effects such as demographic, intrinsic or extrinsic factors, or co-medication on the PK.

The exposure-response relationship between measures of RP-3500 exposure and measures of efficacy, including, but not limited to changes in tumor size, ORR, PFS, and DOR will also be explored.

The relationship between RP-3500 exposure and key safety variable, including ECG, will be explored. In addition, tumor biopsy biomarkers may be explored in the exposure/response analyses.

The population PK/pharmacodynamic and exposure-response analyses will be developed and reported separately from the clinical study report (CSR). Exploratory analysis of the population PK and biomarker changes may also be performed and reported separately from the CSR.



11 INTERIM ANALYSIS

No interim analysis is planned for this study.

12 SAFETY NARRATIVES

Safety narratives will be provided for patients with any of the below events. The actual narrative will be generated based on Safety Narrative Plan.

- Death narratives (All causality)
    - Includes deaths within 30 days after last dose
    - Includes any treatment-related death regardless of the death date
- Treatment-related SAE Narratives
    - Includes any SAEs considered to be related to study drug(s)
    - Excludes any SAEs considered to be related to study procedure/background therapy during Screening
- Narratives of selected SAEs
    - Includes exposure in utero/exposure during breastfeeding cases
- Narratives for permanent discontinuation of treatment due to other reasons than PD (collected in electronic data capture as either radiographic disease progression or physician decision reason – clinical progression), nonserious AEs and deaths.
- Other reasons include:
    - Lost to follow up
    - No longer willing to participate in study
    - Physician decision other than progression (e.g., deteriorated general condition)
    - Other

13 REFERENCES

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APPENDIX 1. RESPONSE EVALUATION CRITERIA N SOLID TUMORS, VERSION 1.1

Evaluation of Target Lesions

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

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

Progressive disease (PD): At least a 20% increase in the sum of the diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

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 study.

Evaluation of Nontarget Lesions

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

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

Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget 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 "nontarget" 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
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 8 weeks from first dose of study medication**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; PD = progressive disease; PR = partial response; RECIST v1.1= Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease

* See RECIST v1.1 manuscript for further details on what is evidence of a new lesion (Eisenhauer 2009).

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-measurable Disease (i.e., Non-target Disease)

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; SD = stable disease.

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

For confirmed overall response the following rules from RECIST v1.1 Table 3 (Eisenhauer 2009) will be applied. A minimum criterion for SD duration of 42 days will be utilized.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

APPENDIX 2. GYNECOLOGICAL CANCER INTERGROUP DEFINITIONS FOR RESPONSE AND PROGRESSION IN PATIENTS WITH OVARIAN CANCER

For patients 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 version 1.1 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 study). Patients 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 2 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 patients with elevated CA-125 pretreatment that normalizes or for patients 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 patients with elevated CA-125 pretreatment 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 CA-125 suggests progression, the patient 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 study.

Patients 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 patients have a CA-125 response but have PD by RECIST v1.1 within 28 days of the CA-125 response, they will be classified as PD
- Patients whose best response by RECIST v1.1 is stable disease but who have a CA-125 response will be classified as CA-125 responders
- For a patient to be classified as a complete responder according to RECIST v1.1, CA-125 levels must be within the normal range

For Patient 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.

For Patients 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.

APPENDIX 3. 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 Appendix 1and will be utilized for evaluation of response in patients 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 nontarget lesions for the assessment.

In addition to RECIST v1.1, patients 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 2 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 2 additional new lesions compared with the first follow-up scan to rule out pseudoprogression (2+2 rule).
- If at least 2 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 2 new lesions were documented.
- Changes in intensity of uptake alone do not constitute either progression or regression.

PSA

For patients 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 postbaseline 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 ≥2 g/mL above the nadir (or baseline for patients 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.