CLINICAL STUDY PROTOCOL SYNOPSIS

Title:	**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)**
Protocol Number:	RP-3500-01
Study Drug Names:	RP-3500, talazoparib, gemcitabine
Development Phase:	1/2a
Sponsor:	Repare Therapeutics 7171 Frederick-Banting Building 2 St-Laurent, Quebec, H4S 1Z9 Canada
Medical Monitor:	Gabriela Gomez, MD, MBA
Indication:	Advanced solid tumors
IND Number:	146,280
EudraCT Number:	2020-000301-87
Date of Original Protocol:	12 March 2020
Date of Amendment 1:	13 July 2020
Date of Amendment 2:	19 November 2020
Date of Amendment 3:	20 May 2021
Date of Amendment 4:	17 August 2021
Date of Amendment 4.1:	26 October 2021
Date of Amendment 5.0:	12 November 2021
Date of Amendment 6.0	14 July 2022
Date of Amendment 7.0	21 June 2024
Version of Protocol:	8.0
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Repare Therapeutics (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

1. SYNOPSIS

Name of Sponsor/Company: Repare Therapeutics	
Name of Investigational Products: RP-3500, talazoparib, and gemcitabine	
Name of Active Ingredients: RP-3500, talazoparib, and gemcitabine	
Title of Study: 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: Treatment Enabled by SNIPRx)*	
Study Duration: Approximately 42 months	**Phase of Development:** 1/2a
Number of Patients (planned): Approximately 451 patients are planned to be enrolled in this study.	

Module 1 Objectives:

Primary Objectives

- To assess the safety and tolerability of RP-3500 in patients with eligible advanced solid tumors
- To define the maximum tolerated dose (MTD) of RP-3500 monotherapy, and determine a recommended Phase 2 dose (RP2D) and schedule

Secondary Objectives

- To assess preliminary anti-tumor activity with RP-3500 in patients with eligible advanced solid tumors
- To characterize the pharmacokinetics (PK) profile of RP-3500
- To assess PK parameters of RP-3500 monotherapy in fasted and fed states
- To assess the relationship between pharmacodynamic biomarkers and PK of RP-3500 in a subset of patients to aid in schedule decisions and assess the correlation with clinical outcomes
- To evaluate the concordance between local and central methods for detecting ataxia telangiectasia-mutated and rad3-related inhibitor (ATRi) sensitizing biomarkers
- To evaluate the impact of treatment with RP-3500 on QT/QTc interval

[redacted]

Module 2 Objectives:

Primary Objectives

- To assess anti-tumor activity of RP-3500 when administered to eligible patients at the RP2D and schedule evaluated in the following arms:
  - ARM 1: Estrogen receptor-positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) breast, ampullary, pancreas, prostate, bile duct, and gastroesophageal junction tumors with likely pathogenic/pathogenic germline ataxia telangiectasia-mutated (ATM) mutations
  - ARM 2: Leiomyosarcoma tumors with ribonuclease H2 (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*

Secondary Objectives

- To determine safety and tolerability of RP2D and schedule in the biomarker-defined patient subsets
- To assess anti-tumor activity of RP-3500 in selected tumors with biallelic versus monoallelic alternations
- To evaluate the preferred assay methods for defining how to select patients for ATRi sensitizing biomarkers for future studies
- To evaluate the concordance between local and central methods for detecting ATRi sensitizing biomarkers.
- To further characterize the PK profile of RP-3500

[redacted]

Module 3 Objectives:

Primary Objectives

- To assess the safety and tolerability of RP-3500 and talazoparib combination in eligible patients with advanced solid tumors
- To define the MTD of RP-3500 and talazoparib combination and determine RP2D and schedule

Secondary Objectives

- To assess preliminary anti-tumor activity of RP-3500 and talazoparib combination in eligible patients with advanced solid tumors

- To assess any PK interaction of RP-3500 and talazoparib when administered in combination
- To determine the pharmacokinetic/pharmacodynamic (PK/PD) relationships of RP-3500 and talazoparib combination to confirm dose/schedule
- To determine activity of RP-3500 and talazoparib combination in patients who progressed after RP-3500 alone

[redacted]

Module 4 Objectives:

Primary Objectives

- To assess the safety and tolerability of RP-3500 and gemcitabine combination in eligible patients with advanced solid tumors
- To define the MTD of RP-3500 and gemcitabine combination and determine RP2D and schedule

Secondary Objectives

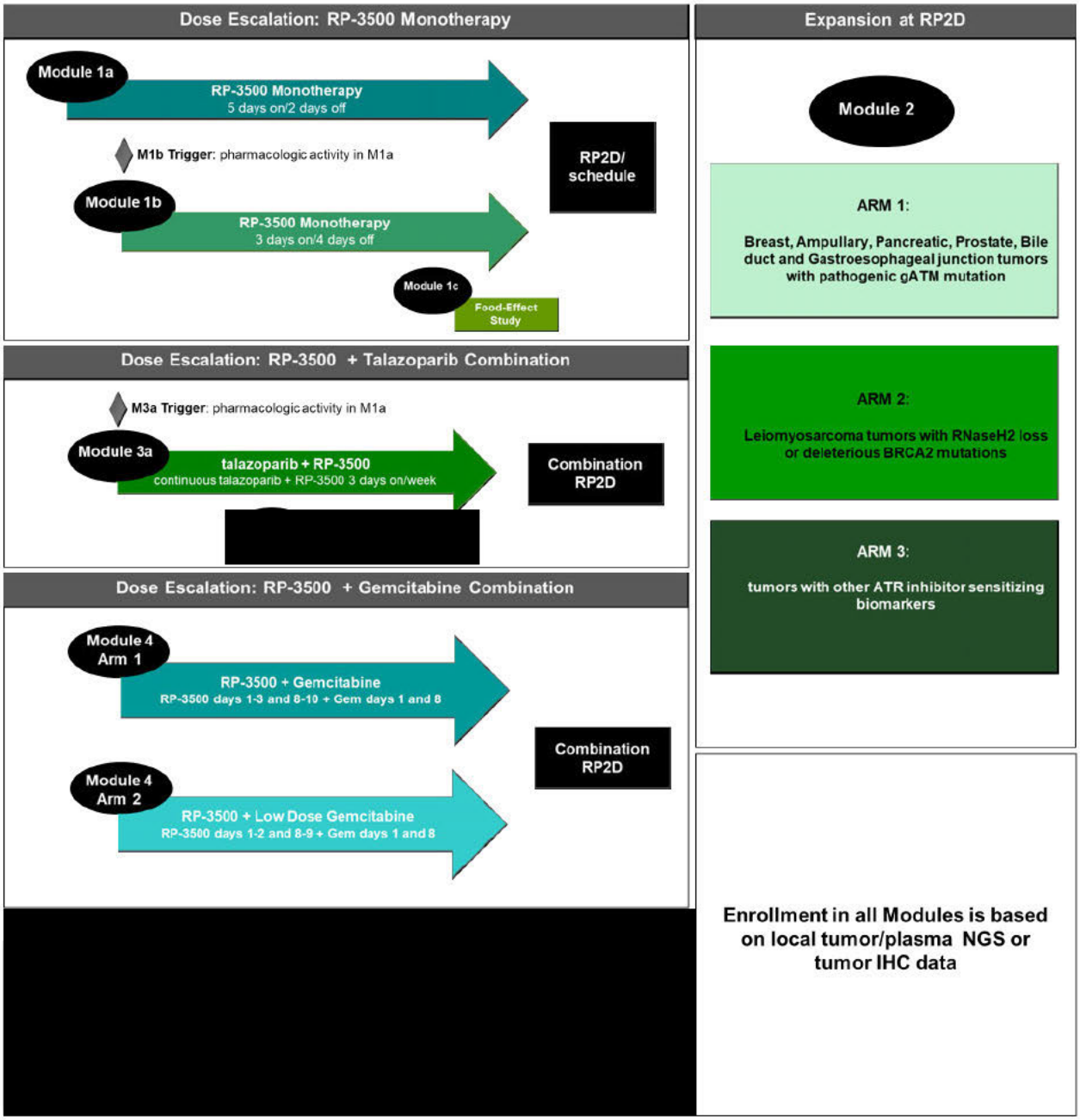
- To assess preliminary anti-tumor activity of RP-3500 and gemcitabine combination in eligible patients with advanced solid tumors
- To assess the PK of RP-3500 when administered in combination with gemcitabine

[redacted]

Study Design:

This is an exploratory modular, Phase 1/2a, first-in-human, multi-center, open-label, non-randomized, 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 ATRi sensitivity. In Modules 1 through 4, approximately 451 patients are expected to be enrolled at approximately 20 sites globally. [redacted]

Study Design Schema:*



** Additional schedules may be tested based on safety, tolerability and drug exposure data.*

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 RP2D and recommended dosing schedule are determined in Module 1. Module 2 (approximately up to 191 additional patients) 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 ATM (gATM) 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 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 4 will evaluate the safety and tolerability of RP-3500 in combination with gemcitabine.

[redacted]

As applicable per module or arm, patients will be enrolled based on local tumor mutation data or Sponsor-approved IHC data (for ATM or RNAseH2) generated in a College of Pathology (CAP)/Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (International Organization for Standardization [ISO] or equivalent) and collected following center-specific institutional guidelines.

Sponsor-approved local next-generation sequencing (NGS) tests include Guardant360®, Caris, Foundation Medicine F1, MSK IMPACT, Oncomine™ V3, Qiagen Comprehensive, or other validated platforms. Germline test results will be accepted from Ambry, Invitae, Myriad, or other tests approved by the Sponsor.

The Precision Oncology Decision Support (PODS) Group at the Khalifa Institute for Personalized Cancer Therapy (IPCT) at the University of Texas MD Anderson Cancer Center (United States [US]) will confirm molecular eligibility for the study prior to start of treatment by comparing NGS CLIA (or equivalent) reports with predefined, Sponsor-approved alterations to ensure NGS results provided by enrolling centers are annotated consistently across all participating centers. This review (uniformly reported by PODS within 72 hours of receiving the report by email) is done to ensure that the patient's tumor molecular profile matches the study eligibility criteria and is uniformly assessed to allow consistent interpretation of data.

The results of nonclinical studies together with early efficacy signals observed in Modules 1 through 5 may support the development of additional study modules to further test RP-3500 in patients with tumors carrying specific genomic alterations, either in monotherapy or in combination with other treatment modalities.

General Study Conduct:

Patient enrollment in Modules 1 through 5 will rely on institutional and Investigator support to identify candidates for RP-3500 therapy and to determine if a patient's tumor is a potential molecular match based on local NGS or IHC data.

The study will consist of a Pre-Screening 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 within 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 (3 months ± 2 weeks from the date of last dose). The treatment period will consist initially of 21-day treatment cycles.

In Module 1a, RP-3500 will be administered initially to 1 patient per dose level once daily (QD) at a starting dose of 5 mg following a 5 consecutive days on and 2 consecutive days off schedule (5/2 schedule). When pharmacologic activity is observed, sufficient patients will be enrolled at that dose level to ensure that safety and tolerability are assessed in at least 2 evaluable patients before a decision for further escalation is made by the SRC. An alternative dosing schedule of 3 days on followed by 4 days off (Module 1b, 3/4 schedule), may be initiated after the dose level that demonstrates pharmacologic activity in Module 1a is confirmed safe by the SRC. If Module 1b is initiated, the starting dose will be the same as the highest total daily dose being evaluated in Module 1a, administered twice daily (BID). Additional schedules may be evaluated that involve intermittent dosing per Module 1a or 1b, with scheduled weeks off to enable bone marrow recovery.

The dose will be increased as appropriate for dose escalation in parallel in both schedule arms until MTD and RP2D are established. Dose escalation decisions will be based on the emerging safety and tolerability profile and clinical PK/PD data across the entire patient population in the study, presented, and discussed regularly at the SRC meetings.

Patients in Module 1c (open only in one US center) will participate in a food-effect evaluation to assess potential differences in RP-3500 exposures and absorption following a standard high-fat meal (up to 12 patients). Patients will 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. 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 as agreed with the Investigator.

At the time of Protocol Amendment 4, enrollment in Module 1c has been completed. The results demonstrated that administration of RP-3500 with a high-fat meal did not result in significant changes to RP-3500 PK that would be expected to impact tolerability or efficacy. Thus, for all patients enrolled as of Protocol Amendment 4, the fasting requirement for RP-3500 will be lifted.

In Module 2, RP-3500 will be administered at a dose level of 160 mg QD on a 3/4 schedule, the RP2D and schedule for monotherapy as established in Module 1.

In Module 3, the RP-3500 starting dose will be one dose level below the highest evaluated daily dose in Module 1a and given initially BID for 3 days only. Patients in Module 3 will initially receive continuous talazoparib at a starting dose of 0.5 mg QD administered orally and escalating BID doses of RP-3500 on days 5, 6 and 7 of every week. As of Protocol Amendment 4, intermittent weekly dosing schedules will be evaluated (eg, 1 week on/1 week off).

In Module 4, RP-3500 will be administered QD at 3 different dose levels (80, 120, and 160 mg) initially in combination with 1000 mg/m^2 gemcitabine. Gemcitabine will be administered on Days 1 and 8, and RP-3500 will be administered on Days 1 to 3 and 8 to 10 in a 21-day treatment cycle. Pending review of safety/tolerability data lower dose levels of gemcitabine and alternative dosing schedules may also be evaluated such as a 1 week on/1 week off dosing schedule of both drugs (this schedule will involve a 28-

day treatment cycle). A Low Dose Gemcitabine (LDG) arm will also be evaluated involving Gemcitabine administration at doses of 100-300 mg/m2 (on Days 1 and 8) in combination with RP-3500 at 120 mg QD on Days 1 to 2 and 8 to 9 (21-day treatment cycle).

[redacted]

RP-3500, talazoparib, and gemcitabine dose adjustments and interruptions are allowed and will follow the recommendations provided in the corresponding sections. Treatment in all modules will continue until disease progression, intolerability of study drugs, Investigator decision, withdrawal of consent, protocol noncompliance or death.

Study procedures:

Study procedures will occur as outlined in the Schedules of Assessments for each module. Safety and tolerability will be followed by the Medical Monitor and evaluated by the SRC throughout the study. Assessments will include clinical and laboratory evaluations, information on adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), physical examinations (PEs), concomitant medications and procedures, vital signs, electrocardiograms (ECGs) and others.

Tumor assessments:

Patients must have a baseline tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of known sites of disease as clinically indicated. Positron emission tomography (PET)/CT may be used as clinically indicated. Additional radiological evaluation, such as diffusion weighted MRI (DW-MRI) or dynamic contrast enhanced MRI (DCE-MRI), may also be used to clarify observations with standard imaging. If the patient has had appropriate imaging scans (eg, routine clinical management) performed within 28 days prior to Cycle 1/Day 1, the results of those scans may be used if they are of diagnostic quality. Subsequent post-baseline tumor assessments will be performed following response evaluation criteria in solid tumors (RECIST) v1.1 guidelines. Response will be assessed by the Investigator. Radiological tests and other measurements used to evaluate efficacy should be stored at the site for up to 12 months after completion of the RP-3500-01 study for possible Independent Radiological Review assessment. If additional imaging is performed (eg, DCE-MRI), this should be continued to properly compare imaging sets.

For follow-up tumor assessments, CT/MRI scans will be performed every 6 weeks (± 7 days) or sooner if clinically indicated, from start of treatment (Cycle 1/Day 1) for the first 3 assessments (first ~5 months/22 weeks on treatment). Thereafter, tumor assessments must be performed every 9 weeks (± 7 days). Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response. The subsequent tumor imaging after the confirmation of response should be obtained per the original scheduled interval from the confirmatory scan (6 weeks ± 7 days during the first ~5 months of study treatment or every 9 weeks thereafter).

For patients with prostate cancer enrolled in Module 2, radionuclide bone scans will also be required at baseline and subsequently at the same frequency as the RECIST tumor assessments as per the Prostate Cancer Working Group 3 (PCWG3) criteria (Appendix 9).

[redacted]

[redacted]

Tumor assessment should occur according to study schedule regardless of whether study drug therapy is interrupted. If a patient discontinues treatment for a reason other than disease progression, withdrawal of consent to study, lost to follow-up, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. In Modules 1, 2, 3, and 4, patients with progressive disease, who are clinically stable, may continue treatment after providing signed written consent, if the Investigator deems that it is in the patient's best interest. The patient may continue receiving treatment in the absence of symptoms or signs indicating clinically significant disease progression: decline in performance status, and rapid disease progression or threat to vital organs requiring urgent medical intervention and significant, unacceptable, or irreversible drug-related toxicity. These patients will be categorized as "PD" and treated only if the investigational drug safety and tolerability is confirmed upon case presentation at SRC.

Laboratory assessments:

Blood samples will be collected in all modules to monitor safety and characterize the PK profile of RP-3500 when administered as a single agent and in combination with talazoparib or gemcitabine.

[redacted]

If specific circulating tumor biomarkers including, but not limited to, cancer antigen 125 (CA-125) or prostate-specific antigen (PSA), are monitored as part of a patient's standard of care to follow the course of their disease, this information will also be collected during Screening (or prior to the first dose on Cycle 1 Day 1) and at least once per cycle throughout treatment and at EOT or as per standard of care. For all patients with prostate cancer enrolled in Module 2 (and those without measurable disease enrolled in the other modules), PSA monitoring at baseline and on Day 1 of every cycle and at EOT will be mandatory as part of the evaluation of response per PCWG3 (Appendix 9). For patients with ovarian cancer enrolled in Module 2, CA-125 measurement will also be mandatory at baseline and on Day 1 of each cycle (through EOT) as part of the evaluation of response per the Gynecological Cancer Intergroup (GCIG) criteria.

Blood samples for the analysis of 4β-hydroxycholesterol, a biomarker of CYP3A induction, and total cholesterol will be collected in patients in Module 1c. This analysis will be conducted at a single center in the US.

Tumor tissue:

To meet primary, secondary[redacted] objectives, a recent archival tumor tissue sample with tumor cell content confirmed by center pathologist at >30% prior to shipping, must be provided. Sites should provide 20 unstained slides (5 µM), along with a hematoxylin and eosin (H&E) stained slide confirming >30% tumor content. The samples must be shipped to the central laboratory during the Screening Period through Cycle 1/Day 1 (+7 days). Patients who do not have archival tumor tissue that meets the specifications detailed in the Laboratory Manual should undergo a fresh tumor biopsy, prior to treatment, if it is considered safe to perform. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval. Please refer to Laboratory Manual for details on tumor sample requirements, collection, preparation, storage, and shipping procedures.

Safety assessments:

AEs will be collected and recorded for each patient from the day of signing the ICF until 30 days after last study drug administration (or until the patient starts a new anticancer therapy, if sooner). Prior to receiving study drug, only AEs considered related to study procedures or SAEs need to be reported. Events that are not serious and not related to a study procedure that occur prior to receiving study drug are to be recorded as medical history. After receiving the first dose of study treatment, information about AEs and SAEs regardless of relationship to the study treatment are reported until 30 days after last study drug administration or until the patient starts a new anticancer therapy, whichever is earlier. Any SAEs that are assessed by the Investigator as related to study treatment should be reported indefinitely (ie, no end to the reporting period).

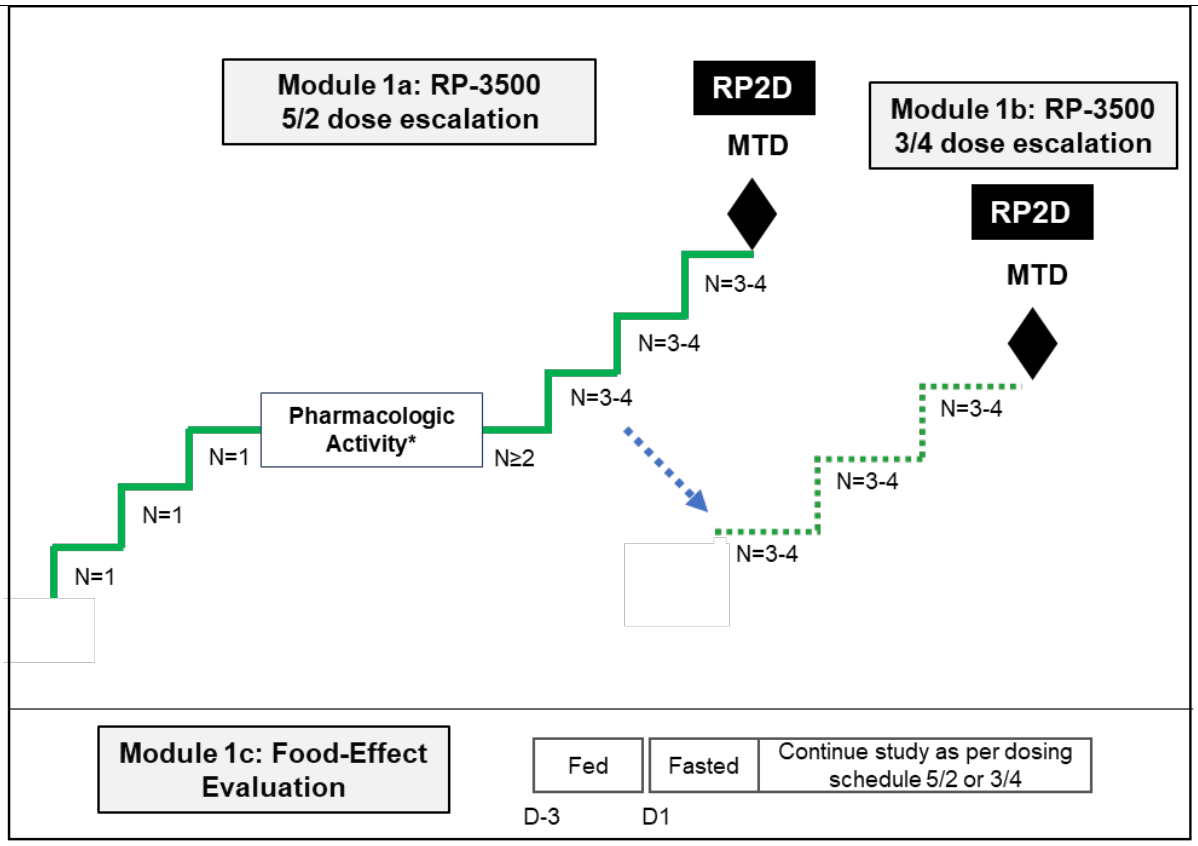
All TEAEs and SAEs experienced by a patient will be monitored until the TEAE or SAE has resolved or returned to baseline or the Investigator has provided a rationale for the observed changes and/or has determined there is no expectation of further improvement, or until the patient is lost to follow-up or has died.

Module 1: RP-3500 Single-Agent, Dose Escalation:

Module 1 will be composed of 3 sub-modules:

- **Module 1a**: 5 days on/2 days off dosing schedule
- **Module 1b**: 3 days on/4 days off dosing schedule
- **Module 1c:** Food-effect evaluation

Module 1 Study Schema:



* 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

Module 1 dose escalation decisions will be governed by the Bayesian optimal interval (BOIN) design. Module 1a and Module 1b will proceed in parallel. Dose escalations will continue independently until the MTD or RP2D is determined for each schedule.

Module 1 cycle duration and DLT observation periods will initially be 21 days (Cycle 1). Each dose escalation decision will be confirmed at the SRC review meeting at the end of each treatment cycle. Dose escalation decisions will be based on the emerging safety and tolerability profile across the entire patient population in the study. Clinical PK/PD data, if available, will contribute to the dose/schedule decisions.

Intra-patient dose escalations will be allowed at the discretion of the Investigator and with Sponsor approval.

Based on the mechanism of action of RP-3500, data from nonclinical animal testing and clinical data from other investigational ATRi agents, and preliminary clinical data from RP-3500, myelotoxicity is an anticipated toxicity and potential DLT following repeated RP-3500 administration. Periodic drug holidays may be required to allow for bone marrow recovery. Patients will be closely monitored during the study. Beyond the DLT period (Cycle 1), study drug interruptions will be allowed for up to 2 weeks. Dose interruptions and dose reductions will be carefully monitored by the SRC. In addition to the intermittent daily dosing schedules specified in Modules 1a and 1b, additional schedules including scheduled weeks off (eg, 2 weeks on/1 week off) will be evaluated with the aim to prevent myelotoxicity and avoid unscheduled dose holds, reductions, and transfusions. In the event that a 3-weeks-on/1-week-off schedule is evaluated, the cycle length will be 28 days. The RP2D and schedule determination will be based on all available data at the conclusion of Module 1, including but not limited to, longer term tolerability of the repeated cycles, required therapy holidays and dose decreases or

transfusions, acute and chronic toxicities, and PK data.

Blood samples will be collected throughout the study to closely monitor safety parameters. Blood samples will be collected prior to and after treatment to evaluate PK of RP-3500 in all Module 1 patients. Blood samples for the analysis of 4β-hydroxycholesterol, a biomarker of CYP3A induction, and total cholesterol will be collected in patients in Module 1c.

[redacted]

Backfill cohorts (up to n=8 patients) at dose levels where the initial treatment effect was observed, may be employed based on agreement with the SRC to enable an earlier and better understanding of the variability in drug-related toxicity, clinical benefit, or PK. The objective of the backfill cohorts is to (1) aid in the assessment of possible anti-tumor activity in a subset of patients with a specific genomic abnormality or tumor type; (2) allow additional PK/PD evaluation and (3) further assessment of drug-related toxicities. Patients enrolled in the backfill cohorts will follow the SOA of the corresponding module and the assessment will be conducted accordingly. [redacted] To avoid exposure of patients to sub-therapeutic doses, the backfill cohorts may only be initiated if there is evidence of biological activity (such as drug related toxicity) or there are data supporting the dose level is within the predicted therapeutic range (such as clinical benefit) or when the RP2D and schedule are established.

[redacted]

Module 1a:

Eligible patients in Module 1a will initially receive RP-3500 QD at a starting dose of 5 mg, at the 5/2 dosing schedule. Dose escalation and de-escalation decisions will be based on the BOIN criteria and dose escalation and de-escalation rules as follows:

- Dose escalation will progress with 1 patient per dose level with dose escalation increments of 100% until pharmacologic activity is observed (level N in Dose Level Table presented below). At this point, sufficient patients will be enrolled at that dose level to ensure that safety and tolerability are assessed in at least 2 evaluable patients, before a decision for further escalation is made by the SRC.
- Dose escalation will continue with increments of 20% to 70% (N+1), enrolling 3 to 4 patients per cohort and dose decisions will depend on 2 or more evaluable patients completing the treatment cycle.
- Non-compartmental analysis will be utilized to analyze the RP-3500 PK parameters throughout the dose escalation phase. If the median human PK exposure required for target

inhibition and efficacy at 24 hours in nonclinical models is exceeded, and pharmacologic activity is still not observed, the dose escalation increments will be reduced to 50% or less. Discretion taking into consideration the PK values and presence, or absence of tumor responses will contribute to the degree of dose escalation in the absence of safety signal.

- If BOIN escalation criteria are met but Grade ≥3 drug-related toxicity (but not DLT) has been observed at the current or lower doses, escalation increments will be limited to 20-50%.
- In the event of dose de-escalation, the next dose level will be at least 30% lower than the current dose (rounded down based on capsule strength) or de-escalated down to the highest previously tolerated dose based on review of the toxicity patterns by SRC. In addition to decreasing the daily dose level, dose de-escalation can involve a reduced frequency of dosing (eg, 2 weeks on/1 week off) at the same daily dose level.

Dose Levels Table*:

Dose Level	5/2 Dose Schedule (Module 1a)		3/4 Dose Schedule (Module 1b)	
	Daily (mg) or % of previous dose increment	**Number of patients**	**Daily (mg) or % of previous dose increment**	**Number of patients**
1 **	5 mg	1	-	-
2 **	100% increment until level N	1	-	-
N (pharmacologic activity observed)	Expand dose	2+	-	-
N+1	20-70 % increments or 20-50% increment if Grade ≥3 drug-related toxicity	3+	Same dose as 5/2 schedule (Module 1a) for 3 days only	3+
N+2	as above	3+	20-70 % increments or 20-50% increment if Grade ≥3 drug-related toxicity	3+
N+3, etc.	as above	3+	as above	3+

**Modules 1a and 1b schedules will progress independently.*
*** Level 1 or 2 may be already level N if early pharmacologic activity is observed.*

Based on the outcome of PK evaluation in the initial dose levels (minimum of 3 dose levels), a consideration for BID) drug administration will be discussed with the SRC. The decision to dose BID will be based on patient outcomes (eg, absence of evidence of hematologic toxicity, tumor response, or other pharmacologic activity) and PK parameters such as, but not limited to, $t_{½}$ <12 hours or a C_{max}:C_{min} ratio >10. The same dose escalation/de-escalation rules will apply for BID dosing cohorts. If BID dosing is initiated, the SRC can elect to continue enrolling patients on a daily dosing arm or cease enrollment on this arm based on the data collected.

Module 1b:

Module 1b (3/4 schedule) may be initiated after a dose level that demonstrates pharmacologic activity in Module 1a is confirmed safe and tolerable by the SRC.

Module 1b starting dose will be the highest daily dose being evaluated in Module 1a but administered only for 3 days each week. Initially, Module 1b will start with RP-3500 administered BID, but a QD schedule could be explored if significant toxicity is observed or PK data instructs. Module 1b will start with cohorts of 3 to 4 patients and dose increments as outlined in Dose Levels Table.

Subsequent dose escalations will continue, enrolling 3 to 4 patients per cohort and dose decisions will depend on 2 or more evaluable patients completing the treatment cycle. Module 1b will follow the same safety rules and dose escalation and de-escalation described in Module 1a.

Module 1c: (open only in one US center)

Module 1c will evaluate the effect of food on the systemic exposure to RP-3500 following a single dose of RP-3500 administered under fed conditions, relative to a single dose of RP-3500 administered under fasted conditions when given to patients with advanced solid tumors.

Module 1c will be initiated at a RP-3500 dose level approved by the SRC that has been determined safe and to have adequate pharmacologic activity. Up to 12 patients will be evaluated to generate data on the potential effects of food on RP-3500 exposures.

On Day -3 and following an overnight fast, patients will be given a standard high-fat breakfast 30 minutes prior to administration of a single dose of RP-3500. On Day 1, following an overnight fast, patients will receive the same RP-3500 dose in a fasted state. Patients will then continue on study following the dosing schedule of Module 1a (5/2) or Module 1b (3/4) at the highest evaluable dose level as agreed with the Investigator. If a BID dosing regimen is implemented, then BID dosing will be initiated on Day 2, following serial PK collections on Day 1.

Module 2: RP-3500 Monotherapy to Establish Preliminary Efficacy in Patients with Tumors Carrying ATRi Sensitizing Mutations

The purpose of the expansion cohorts in Module 2 is to better characterize the anti-tumor activity of RP-3500 at the RP2D and recommended schedule, when administered to patients with tumors assigned to pre-defined molecular subsets and to determine if the subsets warrant further development. Based on the results of Module 1, the selected RP2D for Module 2 is 160 mg QD, administered on a 3/4 schedule.

Patients in Module 2 will be assigned into the following arms:

- **ARM 1**: ER+/HER2- breast, ampullary, pancreas, prostate, bile duct, and gastroesophageal junction tumors with likely pathogenic/pathogenic gATM mutations
- **ARM 2**: Leiomyosarcoma tumors with RNASEH2 loss or deleterious/likely deleterious BRCA2 mutations
- **ARM 3**: Tumors with loss of other ATRi sensitizing biomarkers

For Arm 1, patient enrollment will be based on local or central test results for pathogenic gATM mutations. For patients with ATM mutations identified by NGS in tumor or liquid biopsy samples without known germline mutation status, a blood sample will be collected for germline testing by either a local or a Sponsor-approved test to confirm the presence of a likely pathogenic/pathogenic gATM mutation prior to enrollment. The aim will be to enroll approximately 5 to 8 patients with each tumor type for a total of 42 patients initially. Up to 3 additional expansion cohorts (8 patients each) may be

evaluated. Therefore, the total sample size for Arm 1, including potential expansion cohorts, will be up to 66 patients.

For **Arm 2**, leiomyosarcoma tumors with BRCA2 mutations will be identified using existing NGS data (tumor or germline). Tumors with suspected RNASEH2 loss will be confirmed prior to enrollment by a Sponsor-approved IHC assay, run in a CAP/CLIA laboratory. The aim will be to enroll at least 13 patients with RNASEH2 loss tumors and approximately 5 to 8 patients with BRCA2 mutations for a total of up to 21 patients. As of Protocol Amendment 6.0, this arm is closed for further enrollment and thus expansion cohorts will no longer be considered.

For **Arm 3**, enrollment will be based on local NGS data only, since IHC assays for these genes are not currently validated or available. Enrollment into this arm will include deleterious or suspected deleterious genetic alterations in the following genes: *ATRIP, CHTF8, FZR1, MRE11, NBN, RAD17, RAD50, RAD51B/C/D, REV3L, SETD2, and other genes agreed upon between the Sponsor and Investigator*.

To explore preliminary efficacy across genotypes, Arm 3 will aim to enroll at least 5 and up to 8 subjects per genotype/group. MRE11/NBN/RAD50, and RAD51B/C/D will be considered each as 1 group for a total of 8 genotype groups. A total of 80 patients will initially be treated. Based on efficacy signal, up to 24 additional patients (3 expansion cohorts based on specific genotype) may be evaluated. Therefore, the total sample size for Arm 3, including potential expansion cohorts, will be up to 104 patients. In the event that certain cohorts in any of the arms are slow to enroll based on the rarity of the tumor type/genotype and inclusion/exclusion criteria, the Sponsor may decide to terminate the study prior to completion of the planned enrollment in each group.

For all arms, central confirmation of local NGS will follow retrospectively to support secondary [redacted] endpoints.

Due to heterogeneity within tumor types and genotypes (eg, zygosity, specific molecular alterations), expansion cohorts may be evaluated to better understand responsiveness to RP-3500 in particular patient subsets in which preliminary signs of anti-tumor activity were observed. The expansion cohorts will help to guide in the selection of the appropriate patient population for further evaluation. No formal hypothesis testing will be performed for Arm 3 and at the conclusion of the expansion cohorts for all arms. The decision to open an expansion cohort will require SRC approval.

Module 3: RP-3500 and Talazoparib Combination

The primary objectives of Module 3 are to establish a safe and well-tolerated RP2D for the combination of talazoparib and RP-3500 and to evaluate preliminary signs of efficacy.

Eligible patients will initially receive a continuous dose of talazoparib starting at 0.5 mg QD throughout each 21-day treatment cycle. RP-3500 will be administered BID on Days 5, 6, and 7 of every week. As of Protocol Amendment 4, RP-3500 and talazoparib will be administered on an intermittent weekly schedule (eg, 1 week on/1 week off) due to poor tolerability of the continuous dosing schedule. Cycle length will be 28 days for the 1 week on/1 week off schedule. Additional schedules (eg, 1 week on/2 weeks off) will be tested as needed. Module 3 will be conducted in parallel with Modules 1a and 1b.

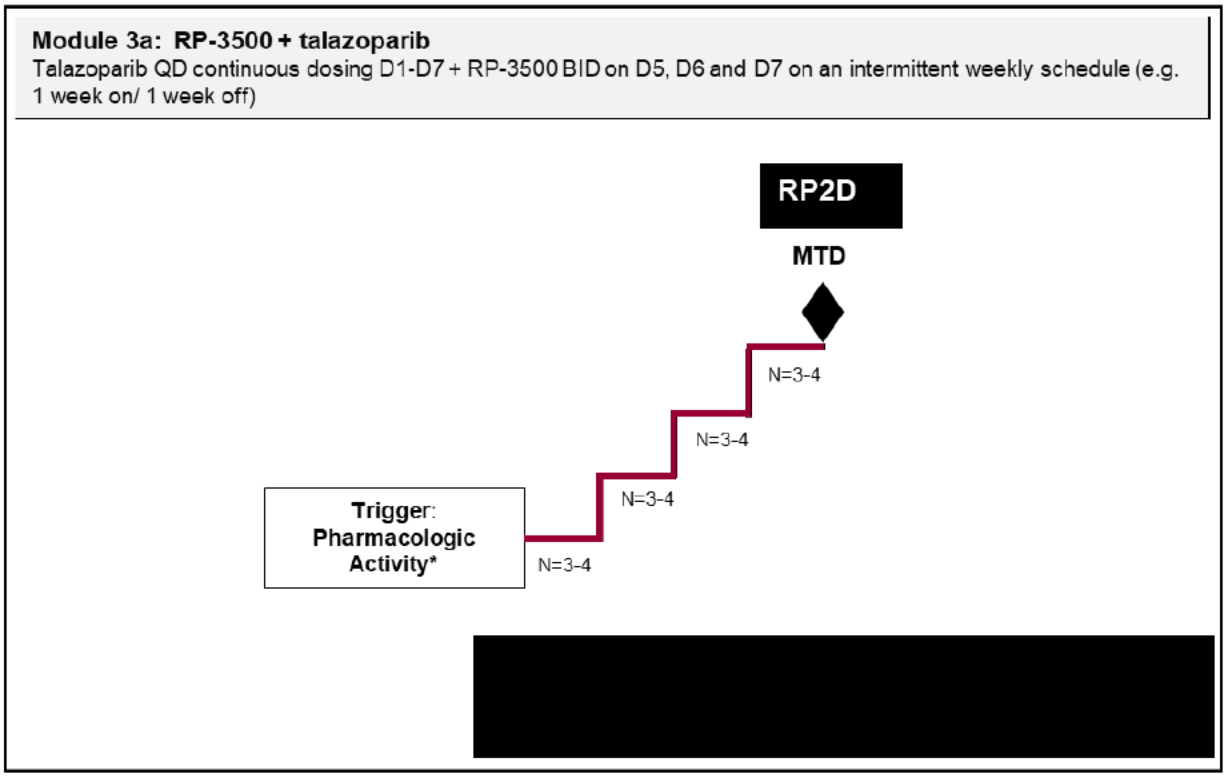
This initial lower dose exploration was chosen to investigate the nonclinically observed synergy in specific genetic backgrounds and desire to develop dose-response and dose-toxicity curves including lower doses. Nonclinical data suggest that substantially lower doses may be needed for therapeutic effect alleviating the overlapping hematological toxicity of ATRi and PARP inhibitor (PARPi) combination.

Module 3 will be composed of 2 cohorts:

- **Module 3a (Main Cohort):** Patients will receive administration of talazoparib on Days 1-7 in combination with RP-3500 on Days 5, 6 and 7 on an intermittent weekly schedule (eg, 1 week on/ 1 week off).

[redacted]

Module 3 Study Schema:



* 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

Module 3 cycle duration and DLT observation periods will initially be 21 days (Cycle 1). Alternative dosing schedules involving a 28-day treatment cycle length may be evaluated. Dose escalation decisions will be governed by the BOIN design and confirmed at the SRC review meetings at the end of each treatment cycle. The emerging RP-3500 safety and tolerability profile observed in Module 1 (RP-3500 monotherapy) and clinical PK/PD data will contribute to all dose escalation decisions in Module 3.

Intra-patient dose escalations will be allowed at the discretion of the Investigator and with Sponsor approval.

Hematological toxicity has been observed in RP-3500 nonclinical studies and talazoparib clinical studies. Due to overlapping toxicities, it is expected that drug reduction and/or interruptions may be required to allow the recovery of bone marrow in patients treated with the combination. Beyond the DLT period (Cycle 1) dose reductions and up to 2 weeks study drug holiday will be allowed. Dose interruptions and dose reductions will be carefully monitored by the SRC.

The RP2D and schedule determination will be based on all available data at the conclusion of Module 3, including, but not limited to, longer term tolerability of the repeated cycles, required therapy holidays and dose decreases, transfusions, acute and chronic toxicities, and PK data of RP-3500 in combination with talazoparib.

[redacted]

Backfill cohorts (up to n=8 patients) may be employed based on agreement with the SRC to enable an earlier and better understanding of the variability in drug combination-related toxicity, clinical benefit, or PK. The objectives of the backfill cohorts are to: (1) aid in the assessment of possible anti-tumor activity in a subset of patients with a specific genomic abnormality or tumor type, (2) allow additional PK/PD evaluation, and (3) further assess drug combination-related toxicities. [redacted]

Module 3a: RP-3500 with Talazoparib Dose Escalation(s)

Module 3a may begin after a dose level that demonstrates pharmacologic activity in Module 1a (Dose Levels Table, Level N). Initiation of Module 3a will be determined by the SRC and the RP-3500 starting dose will be one dose level below the highest evaluated daily dose in Module 1a but administered BID for 3 days only (Days 5, 6, and 7 of each week). Talazoparib will initially be administered continuously QD at a starting dose of 0.5 mg. As of Protocol Amendment 4, RP-3500 and talazoparib will be administered on an intermittent weekly schedule (eg, 1 week on/1 week off) at a talazoparib starting dose level of 0.25 mg. Additional schedules (eg. 1 week on/2 weeks off) will be tested as needed.

Module 3 will start with RP-3500 BID administration, but a QD schedule could be explored if significant toxicity is observed or PK data instructs.

Module 3 will start with cohorts of 3 to 4 patients.

Dose escalation in Module 3a will continue as follows:

- RP-3500 will be escalated at a 20-70% range. The escalation level will be determined upon discussion with SRC, with the actual increment based on evaluation of safety, tolerability, and PK/PD data from all patients in the study, capsule strength for down-rounding, and any other pertinent information.
- If any patient experiences a Grade ≥3 drug-related toxicity that is not considered dose-limiting, RP-3500 dose escalation increments will be limited to 20-50% depending on the type and duration of the toxicity.
- In the event of dose de-escalation, the next dose level will be at least 30% lower than the current dose (rounded down based on capsule strength) or de-escalated down to the highest previously tolerated dose based on review of the toxicity patterns by SRC. In addition to decreasing the daily dose level, dose de-escalation may also involve a reduction in the

number of weeks of dosing in a given cycle.

- Once the RP2D for talazoparib 0.5 mg + RP-3500 is established, the talazoparib dose may be escalated to 0.75 mg QD with RP-3500 adjusted to at least 1 dose level below. Further escalation of talazoparib will progress only if the RP-3500 dose in the 0.5 mg talazoparib + RP-3500 combination is established at approximately 50% of Module 1b RP2D (3/4 monotherapy) and if no significant, unacceptable, or irreversible toxicities, or DLTs are observed. This is to assure that a presumed meaningful RP-3500 dose (ie, 50% of the RP2D for monotherapy) is included in the combination. Consistently, further escalation to a maximum of 1 mg of talazoparib QD is only allowed if the RP-3500 RP2D dose in the 0.75 mg talazoparib + RP-3500 dose level is established as approximately 50% of Module 1b RP2D (3/4 monotherapy). Prior to any increase in the dose of talazoparib, the SRC will review all the available safety data to ensure a dose escalation is safe and acceptable.
- The dose of RP-3500 in Module 3 will not exceed the RP2D in Module 1b.

In the event of drug interactions or unexpected PK findings additional PK/PD evaluation may be required to establish the most effective combination dose and schedule for RP-3500 and talazoparib.

After the RP-3500 plus talazoparib RP2D and schedule are identified in Module 3, expansion cohorts in eligible patients (n=10-20) with tumor types/genotypes of specific interest based on observed clinical benefit, may be enrolled to confirm the safety and tolerability and further evaluate efficacy of the RP2D and schedule for the combination.

[redacted]

Module 4: RP-3500 and Gemcitabine Combination

The primary objectives of Module 4 are to evaluate the safety and tolerability or RP-3500 when administered in combination with gemcitabine and to establish a safe and well-tolerated RP2D. Preliminary signs of efficacy will also be evaluated. Approximately 70 eligible patients will be enrolled.

Eligible patients will initially receive 1000 mg/m^2 intravenous (IV) gemcitabine on Days 1 and 8 and oral RP-3500 on Days 1 to 3 and 8 to 10 of a 21-day treatment cycle (2 weeks on/1 week off dosing schedule) in Arm 1. Three dose levels of RP-3500 will be evaluated, starting at 80 mg QD with escalations to 120

and 160 mg QD. A DL-1 of 800 mg/m^2 gemcitabine or a DL-2 of 600 mg/m^2 gemcitabine in combination with 80 mg RP-3500 may also be evaluated. Once a safe dose of gemcitabine in combination with 80 mg RP-3500 has been established, further escalation of RP-3500 (up to a maximum of 160 mg QD) may be pursued if recommended by the SRC.

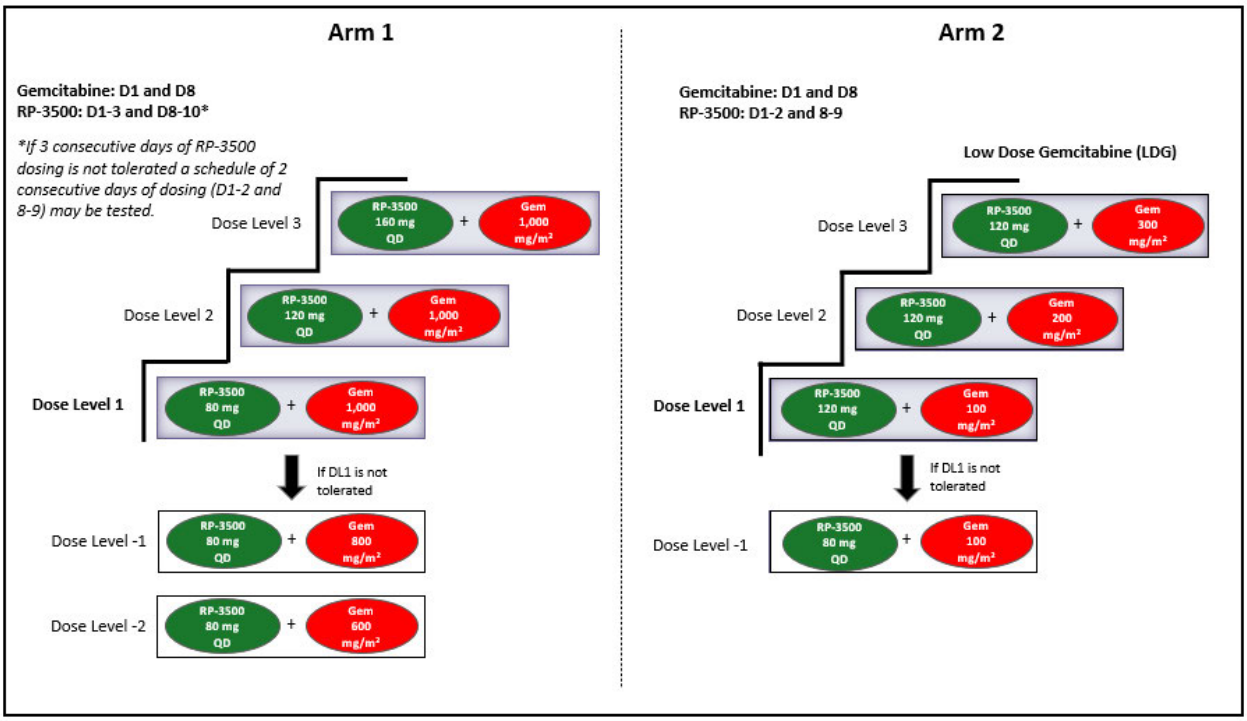
Due to the potential for strong synergy and selective enhancement of cytotoxicity in the appropriate tumor genetic backgrounds when combining low doses of gemcitabine with RP-3500, and in order to avoid dose-limiting neutropenia, a low dose gemcitabine (LDG) arm (Arm 2) evaluating a therapeutic daily dose level of RP-3500 (120 mg QD) in combination with low doses of gemcitabine (≤300 mg/m^2) will also be evaluated. Consistent with preclinical study observations of comparable efficacy and better tolerability, RP-3500 will be administered on a 2 days on/5 days off schedule rather than a 3 days on/4 days off schedule in the LDG arm. Eligible patients will initially receive gemcitabine on Days 1 and 8 in combination with 120 mg RP-3500 on Days 1 to 2 and 8 to 9 of a 21-day treatment cycle. Three dose levels of gemcitabine will be evaluated, starting at 100 mg/m^2 with escalations to 200 and 300 mg/m^2. A DL-1 with 80 mg RP-3500 in combination with 100 mg/m^2 gemcitabine may also be evaluated. Once a safe dose level of gemcitabine in combination with RP-3500 on a 2 days on/5 days off schedule has been identified, a cohort evaluating that gemcitabine dose with RP-3500 on a 3 days on/4 days off schedule may be evaluated if recommended by the SRC.

Additional dose combinations of gemcitabine and RP-3500 (gemcitabine doses between >100 to 500 mg/m^2, RP-3500 dose of up to 160 mg QD) may be tested as warranted by clinical safety/tolerability and efficacy data, as well as emerging nonclinical data, if approved in advance by the SRC.

Due to expected overlapping hematologic toxicities of RP-3500 and gemcitabine, additional treatment schedules may also be evaluated, including reducing the consecutive days of RP-3500 dosing (treatment on D1-2 or D8-9) in Arm 1 or a 1 week on/1 week off schedule of both drugs (to enable bone marrow recovery in between gemcitabine doses) in Arms 1 and 2. In the event that a schedule of 1 week on/1 week off is evaluated, the cycle length will be 28 days. The decision to evaluate these alternative treatment schedules will be driven by review of safety/tolerability data and will require SRC approval.

All Module 4 dose escalation cohorts will enroll 3 to 4 patients per dose level and dose decisions will depend on 2 or more evaluable patients completing the treatment cycle. Dose escalation decisions will be governed by the BOIN design and confirmed at the SRC review meetings at the end of each DLT evaluation period.

Module 4 Study Schema:



Dose Levels of RP-3500 + Gemcitabine

Dose Level	Cycle
Arm 1	
-2*	• RP-3500 80 mg QD (D1-3 and D8-10) • Gemcitabine 600 mg/m^2 (D1 and D8)
-1	• RP-3500 80 mg QD (D1-3 and D8-10) • Gemcitabine 800 mg/m^2 (D1 and D8)
1 (Starting dose level)	• RP-3500 80 mg QD (D1-3 and D8-10) • Gemcitabine 1000 mg/m^2 (D1 and D8)
2	• RP-3500 120 mg QD (D1-3 and D8-10) • Gemcitabine 1000 mg/m^2 (D1 and D8)
3	• RP-3500 160 mg QD (D1-3 and D8-10) • Gemcitabine 1000 mg/m^2 (D1 and D8)
Arm 2 (Low Dose Gemcitabine)	
-1	• RP-3500 80 mg QD (D1-2 and D8-9) • Gemcitabine 100 mg/m^2 (D1 and D8)
1 (Starting Dose Level)	• RP-3500 120 mg QD (D1-2 and D8-9) • Gemcitabine 100 mg/m^2 (D1 and D8)
2	• RP-3500 120 mg QD (D1-2 and D8-9) • Gemcitabine 200 mg/m^2 (D1 and D8)

3	• RP-3500 120 mg QD (D1-2 and D8-9) • Gemcitabine 300 mg/m^2 (D1 and D8)

* Additional lower dose levels of gemcitabine may be evaluated as warranted based on safety/tolerability data. Final decision to escalate or de-escalate will be made by the Safety Review Committee (SRC) based on the dose recommendation by the BOIN method, clinical assessment of toxicity profiles, and PK information observed thus far.

In the event that the scheduled weeks of study drug holiday incorporated are insufficient for adequate recovery from hematologic toxicity, drug reduction and/or interruptions may be required. Beyond the DLT period (Cycle 1), dose reductions and up to 2 weeks study drug holiday will be allowed. Dose interruptions and dose reductions will be carefully monitored by the SRC. Final RP2D for the combination will be established with the SRC based on long-term observation of safety and tolerability of the combination beyond the initial DLT period.

Blood samples will be collected throughout the study to monitor safety parameters. A limited set of blood samples will be collected prior to and after treatment to evaluate PK of RP-3500 in combination with gemcitabine.

Backfill cohorts (up to 8 patients each) may be employed based on agreement with the SRC to: (1) aid in the assessment of possible anti-tumor activity in a subset of patients with a specific genomic abnormality or tumor type, and (2) further assess drug combination related toxicities.

[redacted]

[redacted]

Dose-Limiting Toxicity Criteria (As Assessed During Module 1, Module 3, Module 4[redacted]

Toxicity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 unless otherwise specified. A toxicity will be considered dose-limiting if it occurs during the first cycle and is deemed at least possibly related to study treatment. If multiple toxicities occur, the most severe toxicity will be used in the assessment.

DLTs will be defined as follows:

Treatment-related hematologic AEs:

- Grade 4 neutropenia lasting at least 7 days (Module 4 only: or Grade 3 neutropenia which limits the administration of a scheduled gemcitabine dose)
- Febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of ≥38.3ºC [101°F] or a sustained temperature of ≥38ºC [100.4 °F] for >1 hour)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade ≥2 bleeding
- Grade 4 anemia, or Grade 3 anemia requiring blood transfusion

Treatment-related non-hematologic AEs:

- Any Grade 3 of >24 hours duration
- Any Grade 4 of any duration
- Grade 4 vomiting/diarrhea of any duration that is refractory to supportive care
- *Exclusions: Grade 3 nausea/vomiting/diarrhea unless refractory to supportive care that lasts <3 days, and Grade ≥3 isolated laboratory abnormalities that respond to medical intervention.*

Events that will not be considered a DLT include:

- Grade 3 laboratory abnormalities that are not considered clinically relevant or significant in the opinion of the Investigator
- Grade 3 fatigue with duration of <7 days and resolved to Grade ≤2, unless repeatedly observed and considered drug related upon SRC discussion

Determination of Dose-Limiting Toxicities

The population used for determination of DLTs (MTD, Evaluable Population) will consist of patients who meet the minimum safety evaluation requirements of the study, and/or who experience a DLT.

Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 80% of planned total doses of RP-3500 (Module 1 [redacted]), RP-3500 and talazoparib (Module 3), or 80% of RP-3500 and 100% of gemcitabine (Module 4); and completes all required safety evaluations per Schedule of Assessments; and is observed through the end of Cycle 1.

Dose Escalation and Dose-Limiting Toxicity Assessment

In Modules 1 and 3, dose escalation decisions will be informed by the BOIN design and dose escalation and de-escalation rules. Initially, single patients will be enrolled until a dose that demonstrates pharmacologic activity is observed in Module 1a, at which time sufficient patients will be enrolled at that dose level to ensure that safety and tolerability are assessed in at least 2 evaluable patients, before a decision for further escalation is made by the SRC. Subsequent dose escalations will continue, enrolling 3 to 4 patients per cohort in Module 1 and Module 3. Once cohorts are expanded, at least 2 evaluable patients completing the treatment cycle are required for a dose decision to be made, otherwise, unevaluable patients will be replaced at the same dose level.

Modules 4[redacted] will start with cohorts of 3 to 4 patients (to ensure a minimum of 2 evaluable patients for dose escalation decisions). Subsequent dose escalations (if needed) will continue enrolling ≥3 patients per cohort as governed by the BOIN criteria, and dose decisions will depend on 2 or more evaluable patients completing the treatment cycle.

In Modules 1, 3, 4[redacted] dose escalation decisions will be made by the SRC following the BOIN design and dose escalation and de-escalation rules (see BOIN dose escalation tables, below) and based on the observed safety profile and the emerging clinical PK and available pharmacodynamic data. During dose escalation, the next dose selected will not exceed that allowed by the BOIN criteria.

With the BOIN design re-escalation after de-escalation is allowed. The final decision regarding degree of re-escalation will be determined by the SRC based on the totality of the safety and PK data.

A cohort of up to 8 additional patients may be enrolled to a backfill cohort at the next dose level, after the safety and tolerability decision is reached by SRC for this next dose level.

Dose decisions will be governed by the cumulative number of patients experiencing a DLT at the current dose divided by the cumulative number of patients evaluable for DLT at the current dose. Based on Bayesian statistics and as indicated in the dose escalation decision table, below, if DLT rate is ≤0.197 (<20%), the next cohort of patients will be assigned a higher dose and if ≥0.298 (>30%), the next cohort will be assigned a lower dose. Otherwise, the next cohort will be assigned the same dose. These parameters correspond to a BOIN design with a target rate toxicity of 25% and point hypotheses of 15% for sub-therapeutic toxicity and 35% for excess toxicity.

The resultant dose decisions are displayed in the table below. Note that there may have already been

more than 6 patients exposed at the next dose cohort selected to enable a better definition of the MTD.

Bayesian Optimal Interval Design Dose Escalation Decision Rules for Modules 1, 3, 4

Action	Cumulative Number of Evaluable Patients at Current Dose Level								
	1	2	3	4	5	6	7	8	9
↑ if number of DLT ≤	0	0	0	0	0	1	1	1	1
Stay current dose if DLT	NA	NA	NA	1	1	NA	2	2	2
↓ if number of DLT ≥	1	1	1	2	2	2	3	3	3

Abbreviations: ↑ = *increase;* ↓ = *decrease; DLT = dose-limiting toxicity; NA=not applicable.*
Decisions can be made on larger numbers of patients if necessary.
Note that "# of DLT" is the number of patients with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 evaluable patients.

Dose escalation will stop when 1 of the following criteria are met:

- A total of 140 evaluable patients have been dosed in Module 1 and a total of 50 evaluable patients have been dosed in Module 3a
- A total of 70 evaluable patients have been dosed in Module 4.
- Decision made by the SRC

In the BOIN design, the recommended MTD is defined using isotonic regression. Final decision regarding the MTD and RP2D will be made by the SRC among the doses with a <30% DLT rate.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Written informed consent, according to local guidelines, signed and dated by the patient or legal guardian prior to the performance of any study-specific procedures, sampling, or analyses.
2. Male or female and ≥18 years-of-age at the time of signature of the ICF.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
4. Histologically confirmed solid tumors resistant or refractory to standard treatment and/or patients who are intolerant to standard therapy.
   - Module 2 only: Patients may have had up to 2 prior non-hormonal treatments in metastatic settings or 3 non-hormonal prior treatment regimens if adjuvant was also given. The prior lines of therapy limit will not apply to patients with rare genomic alterations in Arm 3.
5. Measurable disease as per RECIST v1.1.

a. Modules 1, 3, and 4 only: Note: If the patient has non-measurable disease but has an elevated tumor marker(s) (eg, PSA), patient enrollment may be discussed between the Investigator and the Sponsor to obtain formal approval.
b. Module 2: Note: a subset of patients with prostate cancer with non-measurable disease will be considered for enrollment if they have elevated PSA levels (>2 ng/mL) evaluable for response per PCWG3.

[redacted]

6. Existing biomarker profile reported from a local test obtained in a CAP/CLIA, ISO or equivalent laboratory per institutional guidelines:

   - Modules 1, 3, 4[redacted]:
     - Documented and confirmed by central review of local NGS reports by PODS Group, deleterious or likely deleterious genomic alterations for at least 1 of the following genes: *ATM*, *ATRIP*, *BRCA1*, *BRCA2*, *CDK12*, *CHTF8*, *FZR1*, *MRE11*, *NBN*, *PALB2*, *RAD17*, *RAD50*, *RAD51B/C/D*, *REV3L*, *RNAseH2A*, *RNAseH2B*, *SETD2*, or other genes agreed upon between the Sponsor and Investigator.
     - Or documented complete loss of ATM or RNASEH2 protein expression by IHC.
   - Module 2 only:
     - ARM1: ER+/HER2- breast, ampullary, pancreas, prostate, bile duct, and gastroesophageal junction tumors with likely pathogenic/pathogenic gATM mutations
     - ARM 2: Leiomyosarcoma tumors with RNASEH2 loss or deleterious or 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

   [redacted]

   Biomarker results must be reported by a CAP/CLIA or an ISO-accredited laboratory. Plasma or tumor tissue NGS results accepted for all genes except, ATM. Only tumor NGS or evidence of germline alterations are accepted for ATM.

7. Provision of archival tumor tissue sample (or if adequate archival tumor tissue is not available, provision of a fresh biopsy if there is a lesion that can be safely biopsied). Note: If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval.
8. Ability to comply with the protocol and study procedures detailed in the Schedule of Assessments.
9. Ability to swallow and retain oral medications.
10. Acceptable organ function at Screening, as evidenced by the following laboratory data:
    a. Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/min using the Cockcroft-Gault equation or by 24-hour urine collection

[redacted]

b. Total bilirubin ≤1.5 × ULN or <3.0 × ULN if known Gilbert's disease.

c. Serum albumin ≥2.5 g/dL

d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present and thought to be a reason for AST/ALT elevation, in which case they must be ≤5 × ULN

11. Acceptable hematologic function at Screening:

a. No red blood cell or platelet transfusions or growth factors within:

- Module 1: 7 days of the first dose of RP-3500
- Modules 2, 3, 4 [redacted]: 14 days of first dose of study drug/s

b. Hemoglobin:

Module 1: ≥9.5 g/dL

Modules 2, 3, 4 [redacted]: ≥10 g/dL

c. ANC ≥1700 cells/mm^3

d. Platelet count ≥140,000 cells/mm^3

12. Negative pregnancy test for women of childbearing potential (WOCBP) at Screening (serum test only) and prior to the first dose of study drug.

- WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP, who are sexually active, and their partners must agree to use a highly effective form of contraception as detailed in Appendix 3 throughout their participation during study treatment and for 6 months (or 7 months for Module 3 patients) after the last dose of study drug(s).
- Women are considered post-menopausal and not of childbearing potential if they have had no menses for 12 months without an alternative medical cause or are permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

13. Resolution of all toxicities of prior therapy or surgical procedures to baseline or Grade 1 (except for neuropathy, hypothyroidism requiring medication and alopecia which must have resolved to

Grade ≤2). Any prior radiation (with exceptions for palliative radiotherapy) must have been completed at least 7 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of study treatment.

14. Male patients with female partners of childbearing potential must follow a contraception method (oral contraceptives allowed) at least as conservative as Clinical Trial Facilitation Group (CTFG) recommendations (Appendix 3) during their participation in the study and for 6 months following last dose of study drug. Male patients must also refrain from donating sperm during their participation in the study and for 6 months following last dose of study drug.
15. Life expectancy ≥12 weeks after the start of the treatment according to the Investigator's judgment.

Additional Inclusion Criteria for Module 1c:

16. Ability to consume a high-fat meal and fast for 12 hours.

[redacted]

Exclusion Criteria:

1. Chemotherapy, small molecule anticancer or biologic anticancer therapy given within 14 days prior to first dose of study drug. For patients with breast or prostate cancer continuation of long-term luteinizing hormone-releasing hormone (LHRH) or gonadotrophin releasing hormone (GnRH) are allowed if these medications were prescribed for at least 4 months before trial entry.
   - Module 2 only:
     – Patients in Module 2 with ER+/HER2- breast cancer, if they are currently taking anti-estrogen therapy, can remain on the same anti-estrogen therapy while on study. If a patient has been off anti-estrogen therapy for >28 days, they should not restart.
2. History or current condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
3. Prior therapy with an ATR or DNA-dependent protein kinase (DNA-PK) inhibitor.
   a. Module 4 only:
      – Prior therapy with a gemcitabine-containing regimen as the most recent prior line of therapy (prior gemcitabine is allowed if there is at least one intervening therapy).
4. Known hypersensitivity to any of the ingredients of RP-3500.
5. Life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as coagulopathy, encephalopathy or ascites requiring drainage within 4 weeks prior to enrollment) or other reasons which, in the Investigator's opinion, could compromise the patient's safety, or interfere with or compromise the integrity of the study outcomes.
6. Uncontrolled, symptomatic brain metastases. Patients with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms are

controlled and stable), have no evidence of new or enlarging brain metastases, and are clinically stable off steroids for at least 7 days prior to study drug.

7. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg; diastolic BP ≥100 mmHg) despite adequate treatment prior to first dose of RP-3500.
8. Patients with active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness. In equivocal cases, patients whose viral load is negative, may be eligible. HIV seropositive patients who are healthy and low risk for AIDS related outcomes could be considered eligible. Eligibility criteria for HIV positive patients should be evaluated and discussed with Sponsor's Medical Monitor, and will be based on current and past cluster of differentiation 4 (CD4) and t-cell counts, history (if any) of AIDS-defining conditions (eg, opportunistic infections), and status of HIV treatment.
9. Moderate or severe hepatic impairment (ie, Child-Pugh class B or C).
10. History or presence of an abnormal ECG that is clinically significant in the Investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or recent history of myocardial infarction that in the opinion of the Investigator will pose an increased risk of rhythm abnormalities.
11. QT interval corrected using Fridericia's formula (QTcF) >470 msec demonstrated by at least 2 ECGs >30 minutes apart.
12. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (eg, severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
13. Current treatment with medications that are well-known to prolong the QT interval (Appendix 4)
14. History of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) diagnosis
15. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
16. Patients who are receiving strong CYP3A inhibitors or inducers, P-glycoprotein (P-gp) inhibitors and/or breast cancer resistant protein (BCRP) inhibitors within 14 days prior to first dose of study drug.
17. Patients who are pregnant or breastfeeding

Additional Exclusion Criteria for Module 3:

18. Known hypersensitivity to any of the ingredients of talazoparib.

[redacted]

Investigational Product, Dosage and Mode of Administration:

Study drug administration instructions and a dosing diary will be provided to patients to support study drug home dosing.

Twelve patients in Module 1c received a single dose of RP-3500 in a fed and fasted state to determine the need for a fasting requirement prior to RP-3500 administration in subsequent patients and in subsequent modules. **At the time of Protocol Amendment 4, enrollment in Module 1c has been completed. The results demonstrated that administration of RP-3500 with a high-fat meal did not result in meaningful changes to RP-3500 PK that would be expected to impact tolerability or efficacy. Thus, for all patients enrolled on Protocol Amendment 4, the fasting requirement for RP-3500 will be lifted.**

In all modules, RP-3500 is to be orally self-administered with approximately 240 mL (~8 oz) of water. Patients will be initially instructed to take their RP-3500 dose in the morning at approximately the same time each day.

In Module 1a, RP-3500 will be initially administered, QD, at a starting dose of 5 mg, then as appropriate for dose escalation level until RP2D is established. In Module 3 patients will initially receive 0.5 mg of talazoparib QD continuously throughout each 21-day treatment cycle, and RP-3500 will be orally administered BID on Days 5, 6, and 7 of every week. As of Protocol Amendment 4, RP-3500 and talazoparib will be administered on an intermittent weekly schedule (eg, 1 week on/1 week off).

The results from initial PK/PD/efficacy data in Module 1 will instruct dosing levels and schedule for Modules 2, 4[redacted].

In Module 2, RP-3500 will be administered at a dose level of 160 mg QD (3/4), and the schedule and dose will follow dose modifications recommendations.

In Module 4 Arm 1, gemcitabine will be administered initially at a dose of 1,000 mg/m^2 IV on Days 1 and 8 in combination with oral RP-3500 on a 3/4 (Days 1 to 3 and 8 to 10) schedule in a 21-day treatment cycle. In Arm 2 (LDG), gemcitabine will be administered at escalating doses from 100-300 mg/m2 on Days 1 and 8 in combination with RP-3500 on a 2/5 (Days 1 to 2 and 8 to 9) schedule (21-day treatment cycle). A 1 week on/1 week off schedule of both drugs may also be evaluated with either RP-3500 dosing schedule (3/4 or 2/5).

[redacted]

The results of initial PK analysis and RP-3500 half-life from QD dosing will determine the subsequent recommendations for daily dosing frequency. If a BID dosing schedule is evaluated, the dose will be 50% of the highest QD dose currently being evaluated and should be taken approximately 12 hours apart. Any adjustments to the proposed schedule or mode of administration will be discussed and confirmed with SRC and protocol and ICF amended if required.

Dose interruptions and dose reduction to manage toxicities are allowed and will be carefully monitored by the SRC. Beyond the DLT period (Cycle 1) dose reductions and up to 2 weeks study drug holiday will be allowed. Periodic drug holidays may be required to allow for bone marrow recovery. Patients will be monitored weekly during Cycle 1, on Day 1 and Day 15 from Cycle 2 through Cycle 4, at the start of each cycle and as required.

Duration of Treatment

Treatment will continue until disease progression by RECIST v1.1 criteria or PCWG3 for patients with prostate cancer in Module 2 [redacted], intolerability of study drug(s), Investigator decision, consent withdrawal, start of a non-study anticancer treatment, protocol noncompliance or death. Patients will have a Survival Follow-Up assessment that will be done via telephone (or standard method used by participating centers and agreed with Sponsor) 3 months (± 2 weeks) following the last dose unless the patient withdraws consent to the study. In Modules 1 to 4, patients with progressive disease by RECIST v1.1 (or PCWG3 for patients with prostate cancer) criteria, who are clinically stable, may continue treatment after providing signed written consent, if the Investigator deems that it is in the patient's best interest. The patient may continue receiving treatment in the absence of symptoms or signs indicating clinically significant disease progression; decline in performance status; rapid disease progression or threat to vital organs requiring urgent medical intervention and significant, unacceptable, or irreversible drug-related toxicity [redacted]. These patients will be categorized as "PD" and treated only if the investigational drug safety and tolerability is confirmed upon case presentation at SRC.

Endpoints:

Safety:

- DLTs
- Incidence of TEAEs, treatment-related TEAEs, TEAEs leading to death, SAEs, treatment-related SAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose modifications, and TEAEs leading to study discontinuation summarized by system organ class (SOC) and MedDRA preferred term (PT).
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters, PEs and usage of concomitant medications and procedures
- 4β-hydroxycholesterol, a biomarker of CYP3A induction, will be evaluated at a pharmacologically active dose level

Efficacy:

- Overall response rate: best response of CR or PR, based on Investigator's assessment using RECIST v1.1 criteria, or response in CA-125 or PSA (for patients with prostate cancer without measurable disease) as per GCIG or PCWG3.
- Objective response rate (ORR): confirmed best response of CR or PR, based on Investigator's assessment using RECIST v1.1
- Duration of objective response (DOR): based on Investigator's assessment using RECIST v1.1
- Clinical benefit rate: CR + PR + stable disease [SD] ≥4 months, based on Investigator's assessment using RECIST v1.1, CA-125 response by GCIG criteria, or PSA response based on PCWG3 (for patients with prostate cancer without measurable disease).
- Progression-free survival time (PFS) and rate of PFS at 6 months, based on Investigator's assessment using RECIST v1.1

Pharmacokinetics:

Blood samples will be drawn to determine RP-3500 and talazoparib PK parameters. Blood samples will be collected at the timepoints outlined in each module. Blood samples for the analysis of 4β-hydroxycholesterol, a biomarker of CYP3A induction, and total cholesterol will be collected in patients in Module 1c. The PK of gemcitabine will not be assessed in this study.

[redacted]

Statistical Methods

Sample Size Calculation

The maximum total number of patients exposed across Modules 1 to 4 will be 451. The maximum number of patients across Modules 1 and 3 will be 190. Modules 1 and 3 will depend on the number of dose escalations and include up to 8 patients enrolled in any of the backfill cohorts. The maximum number of patients included in the assessment of efficacy in Module 2 will be 191 (including expansion cohorts). This will consist of an initial total sample of 143 patients across 3 different arms and genotype subsets, followed by potentially up to 48 patients from 6 cohort expansions based on observation of efficacy in specific tumor types/genotypes. The number of patients enrolled in Module 4 will be approximately 70. [redacted]

The planned sample size, and the success criteria for Arm 1 and Arm 2 of Module 2, based on the overall response rate (RECIST v1.1, GCIG, and PCWG3), is described in the table below.

Module 2 Efficacy Cohort Success Criteria for Arm 1 and Arm 2

Arm	Total N	Success Criteria for Overall Response Rate	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; p0 = the null hypothesis for ORR, the minimal level of efficacy required; p1 = the alternative hypothesis for ORR, the desired level of efficacy; Pet-p0 = probability of early termination with a true ORR of p0

Success criteria are defined as the total number of responses 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 arm.

All designs have 1-sided alpha of <5% and ≥80% power utilizing a 2-stage 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, arm-specific success criteria are defined in terms of the number of responses needed to be observed, from the required number of patients. Due to preliminary Module 1 results showing prolonged stable disease and slow declines in tumor size in patients with ATM mutant tumors, the futility criteria will also take into consideration of clinical benefit rate in determining whether the study should continue to fulfill enrollment with the target sample size. The final success criteria for the hypothesis testing may be adjusted to ensure the overall type I error is reasonably controlled.

Sensitivity analyses will be performed to assess the effect of including Module 1 efficacy patients who met the eligibility criteria of Module 2.

The initial planned sample size for Arm 3 is 80. Due to the heterogeneity of this patient population, no formal hypothesis testing will be performed for Arm 3 of Module 2. If a cohort expansion is added based on efficacy signal in specific tumor types/genotypes, only descriptive statistics will be provided for hypothesis generating purpose.

Module 2 expansion cohorts with up to 8 patients per cohort may be enrolled. Therefore, the maximum number of patients will be 66 for Arm 1 (up to 3 expansion cohorts), 21 for Arm 2, and 104 for Arm 3 (up to 3 expansion cohorts). No formal hypothesis testing will be performed at the conclusion of the expansion cohorts.

The following analysis populations will be used:

- The primary analysis population for dose decisions within Modules 1, 3, 4[redacted] will be the **DLT Evaluable Population** consisting of patients who receive at least 80% of planned total doses of RP-3500 (Modules 1[redacted]), 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; or patients who experience a DLT. This population will be applied to dose escalation decisions in Modules 1, 3, 4[redacted].
- The **Efficacy Population** used for the assessment of efficacy for Phase 2 module (Module 2), will consist of all patients who received at least 1 dose of RP-3500, evaluable for response by RECIST v1.1 and/or GCIG CA-125 criteria or PCWG3 PSA criteria or discontinued early due to clinical progression or death prior to any post-baseline tumor assessment. The Efficacy Population used for the assessment of efficacy for Phase 1 modules (Modules 1, 3, 4[redacted]) will consist of all patients who receive at least 1 dose of RP-3500, are evaluable for post-baseline response by radiographic tumor assessment and/or tumor marker assessment by GCIG CA-125 criteria or PCWG3 PSA criteria.
- The **Safety Population**, used for the assessment of overall safety and tolerability, will consist of all patients who receive at least one dose of RP-3500.
- The **Pharmacokinetic Population**, used for the assessment of PK endpoints, will consist of all patients who have sufficient PK RP-3500 (and talazoparib where applicable) concentration data recorded to derive PK endpoints.

The primary efficacy endpoint of overall response rate is defined as the proportion of patients with best response of CR or PR according to RECIST v1.1 criteria based on the Investigator's assessment, [redacted] CA-125 response based on GCIG criteria, or PSA response based on PCWG3 (for patients with prostate cancer without measurable disease). 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.

Depending on responses seen, a central review of all images may also be performed by an independent reviewer as a sensitivity analysis. More details on the statistical analysis can be found in the Statistical

Section.

Safety Analysis

All AEs will be listed, including the verbatim description and MedDRA PT and system organ class (SOC). TEAEs are defined as those occurring after the first dose of study drug and within 30 days following the cessation of treatment or until start of new anticancer therapy, whichever is earlier.

Incidence of TEAEs, treatment-related TEAEs, TEAEs leading to death, SAEs, treatment-related SAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose modifications, and TEAEs leading to study discontinuation will be evaluated by dose and schedule for each Module and pooled across Modules 1 and 2 where applicable for the Safety Population.

TEAEs will be further summarized by severity (according to NCI CTCAE Version 5.0). Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, ECG parameters, physical examinations and usage of concomitant medications and procedures. In addition, DLTs will be summarized by schedule and Cycle 1 dose level in Modules 1, 3, 4[redacted] for the DLT Evaluable Population.

PK Analysis:

PK parameters for RP-3500 and talazoparib (when applicable) will be calculated using non-compartmental analysis or modeling methods as well as using a population PK model: area under the concentration-time curve (AUC) from time 0 to last quantifiable concentration ($AUC_{0\text{-last}}$); AUC from time 0 to 8 hours post dose ($AUC_{0\text{-}8}$); AUC from time 0 to infinity ($AUC_{0\text{-inf}}$); maximum observed plasma concentration (C_{max}); time to reach C_{max} (t_{max}); and terminal elimination half-life ($t_{1/2}$) will be calculated along with additional parameters as needed.

The effect of food on exposure to RP-3500 will be assessed by a comparison of geometric mean ratios (GMR) and the 90% confidence intervals of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}.

The effect of gemcitabine or talazoparib on the PK of RP-3500 will be assessed as a co-variate in the population PK model where appropriate.

[redacted]

2. TABLE OF CONTENTS

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

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on 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 one or more new lesions is also considered progressions).

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

Table 1: For Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	>4 wks. Confirmation[b]
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation[b]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once 8 wks. from first dose of study medication[b]
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD[c]	Yes or No	PD	
Any	Any	Yes	PD	

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

a See RECIST v1.1 manuscript for further details on what is evidence of a new lesion [Eisenhauer 2009].

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

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

Note: 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.

Table 2: For Patients with Non-Measurable Disease (ie, Non-Target Disease)

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

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

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

APPENDIX 3. CONTRACEPTIVE GUIDELINES

Patients of childbearing potential, who are sexually active, and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 6 months (or 7 months for Module 3 female patients) after the last dose of study drug(s):

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence if it is the preferred and usual lifestyle of the patient

Source: Clinical Trials Facilitation and Coordination Group (CTFG) 2014.

APPENDIX 4. CONCOMITANT MEDICATIONS ASSOCIATED WITH A RISK OF QTC INTERVAL PROLONGATION AND/OR TORSADES DE POINTES

RP-3500 has not demonstrated adverse effects on QT-prolongation in studies to date, however caution is advised when administering RP-3500 with any drug that may prolong QT.

A vast number of medications prolong the QT interval. They are preferably classified based on the degree of QT prolongation they induce. This is specifically medication dependent. For example, many commonly used medications, such as diphenhydramine and azithromycin, exhibit QT-prolonging effects. However, the degree of QT prolongation is not severe enough to warrant caution in healthy patients. These medications bind to the human ether-related gene (hERG) channels and reduce electrical conduction through the potassium ion channels. This results in delayed repolarization of the heart.

Caution is advised when combining QT-prolonging medications or when using these medications in patients with electrolyte abnormalities. Below is a list of potential medications that may prolong QT interval. Patients receiving medications classified as “know risk” should be excluded. Please reach out to the Medical Monitor prior to enrolling any patient on RP-3500 or starting them on new medication while on study that you believe may prolong QT. Additionally, consulting with your local pharmacist is advised.

Risk	Drug Categories				
	Antiarrhythmic Drugs	Common Antibacterial and Antifungal Drugs	Prokinetic and Antiemetic Drugs	Antipsychotics	Antidepressants
Known risk	Amiodarone Disopyramide Dofetilide Dronedarone Flecainide Ibutilide Procainamide Quinidine Sotalol	Moxifloxacin Levofloxacin Ciprofloxacin Clarithromycin Erythromycin Azithromycin Fluconazole Pentamidine	Domperidone Chlorpromazine Ondansetron Droperidol	Haloperidol Mesoridazine Thioridazine Pimozide	Escitalopram Citalopram
Possible risk		Telavancin Telithromycin Gemifloxacin Norfloxacin Ofloxacin	Dolasetron Granisetron Promethazine Tropisetron	Lithium Clozapine Paliperidone Risperidone Promethazine Perphenazine Pimavanserin Iloperidone Aripiprazole Asenapine	Clomipramine Desipramine Imipramine Mirtazapine Nortriptyline Trimipramine Venlafaxine
Conditional risk	Ivabradine	Amphotericin B Itraconazole Ketoconazole Metronidazole Posaconazole Voriconazole Cotrimoxazole (avoid in congenital long QT syndrome)	Metoclopramide	Quetiapine Olanzapine Ziprasidone	Amitriptyline Doxepin Fluoxetine Fluvoxamine Paroxetine Setraline Trazodone
Alternatives		Penicillin Cephalosporins Doxycycline Anidulafungin	Aprepitant Fosaprepitant Palonosetron	Brexpiprazole	Desvenlafaxine Bupropion (except in supratherapeutic dose) Vortioxetine Vilazodone Levomilnacipran Milnacipran

Note: Known risk of torsades de pointes (TdP): These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended and should be excluded. Possible risk of TdP: These drugs can cause QT prolongation but lack evidence for a risk of TdP when taken as recommended. Conditional risk of TdP: These drugs could cause TdP only under certain conditions, such as excessive dosing, electrolyte imbalance, and interacting with other drugs that can cause TdP. Alternatives: Drugs that at this point have not been linked to clinically significant QTc prolongation. (Please see http://crediblemeds.org for an exhaustive list.)
Ondansetron is only prohibited if administered as a single intravenous dose of >16 mg. Oral administration is allowed.
Source: Porta-Sánchez 2017

APPENDIX 5. STRONG CYP3A INHIBITORS AND INDUCERS, P-GP INHIBITORS, AND BCRP INHIBITORS

Table 3: Strong CYP3A Inhibitors

Inhibitor	**Therapeutic Class**
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
troleandomycin	Antibiotics
telaprevir	Antivirals
itraconazole	Antifungals
indinavir	Protease Inhibitors
voriconazole	Antifungals
mifepristone	Antiprogestins
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice	Food Products
ceritinib	Kinase Inhibitors
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors
boceprevir	Antivirals

Table 4: Strong CYP3A Inducers

Inducers	**Therapeutic class**
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens

Inducers	**Therapeutic class**
ivosidenib	Cancer Treatments
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's Wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
phenobarbital	Anticonvulsants

P-gp Inhibitors:

amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ranolazine, ritonavir, telaprevir, verapamil

BCRP Inhibitors:

curcumin, cyclosporine A, eltrombopag

APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken 1982

APPENDIX 9. 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 1 and 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 1.1 is that bone lesions will not be recorded as target or non-target lesions for the assessment.

In addition to RECIST 1.1, 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 two or more new lesions compared with the baseline bone scan after the 12-week flare window.
- If the new lesions occur within the first 12 weeks of treatment, assessment of progression requires a confirmatory scan performed 6 or more weeks later showing two additional new lesions compared with the first follow-up scan to rule out pseudoprogression (2+2 rule).
- If at least two additional new lesions are seen on the next (confirmatory) scan performed after the 12-week flare window, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented.
- Changes in intensity of uptake alone do not constitute either progression or regression.

PSA

For 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 post-baseline PSA result, with a consecutive assessment conducted at least 3 weeks later.

Assessment for progression:

- PSA progression is defined as a PSA increase ≥25% and ≥2g/mL above the nadir (or baseline for 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.

Reference

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al; Prostate Cancer Clinical Trials Working Group 3. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J clin Oncol. 2016;34(12):1402-18.

APPENDIX 10. 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 (RECIST) v1.1 criteria as per Gynecological Cancer Intergroup (GCIG) criteria [Rustin 2011].

Definition of Response by CA-125

- A ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 3 weeks (note that GCIG recommends maintenance for at least 28 days; a modification was made based on the 3-week cycle length in this 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 two weeks before starting treatment.
- Intervening samples and the confirmatory sample must be less than or equal to the previous sample (within an assay variability of 10%).
- The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.
- A CA-125 complete response can occur if CA-125 levels fall to within the reference range.

Definition of Progression by CA-125

- For patients with elevated CA-125 pre-treatment 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 pre-treatment which never normalizes: CA-125 at least 2 times the nadir value on 2 occasions at least 1 week apart.
- Progressive disease (PD) by objective change in tumor size should always take precedence over changes in CA-125 should it occur first. If measurable disease is reducing in size but the 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 within 28 days of the CA-125 response, they will be classified as PD.
- Patients whose best response by RECIST is stable disease (SD) but who have a CA-125 response will be classified as CA-125 responders
- For a patient to be classified as a complete responder according to RECIST, CA-125 levels must be within the normal range

Table 1: For Patients with Measurable Disease

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

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

Table 2: 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.

Reference

Rustin GJS, Vergote I, Elizabeth E, Pujade-Laurane E, Quinn M, Thigpen T, et al; Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011; 21(2):419-2.