NCT#: NCT04972110

CLINICAL STUDY PROTOCOL SYNOPSIS

Title:	**Phase 1b/2 Study of ATR InhibiTor RP-3500 and PARP Inhibitor Combinations in Patients with Molecularly Selected Cancers (ATTACC)**
Protocol Number:	RP-3500-03
Study Drug Names:	RP-3500, niraparib, olaparib
Development Phase:	1b/2
Sponsor:	Repare Therapeutics 7210 Frederick-Banting, Suite 100, St-Laurent, Quebec, H4S 2A1 Canada 101 Main Street, 16th Floor, Suite 1650, Cambridge, MA 02142 USA
Medical Monitor:	Gabriela Gomez, M.D., M.B.A.
Indication:	Advanced solid tumors
IND Number:	146,280
Date of Protocol:	11 February 2021
Date of Amendment 1:	19 February 2021
Date of Amendment 2:	17 March 2021
Date of Amendment 3:	1 April 2021
Date of Amendment 4:	7 April 2021
Date of Amendment 5:	17 December 2021
Date of Amendment 6:	21 September 2022
Date of Amendment 7:	15 February 2023
Version of Protocol:	8.0
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use and all applicable local Good Clinical Practice (GCP) guidelines and regulations. All required study documentation will be archived as required by regulatory authorities.

1. SYNOPSIS

Name of Sponsor/Company: Repare Therapeutics	
Name of Investigational Products: RP-3500, niraparib, olaparib	
Name of Active Ingredients: RP-3500, niraparib, olaparib	
Title of Study: Phase 1b/2 Study of ATR InhibiTor RP-3500 and PARP Inhibitor Combinations in Patients with Molecularly Selected Cancers (ATTACC)	
Study Duration: Approximately 24 months	**Phase of Development:** 1b/2
Number of Patients (planned): Approximately 196 evaluable patients are planned to be enrolled in this study.	

Hypotheses:

Concomitant administration of the ataxia telangiectasia-mutated- and rad3-related inhibitor (ATRi) RP3500 and the poly (adenosine diphosphate-ribose polymerase) inhibitor (PARPi) niraparib or olaparib at low and intermittent doses has an acceptable toxicity profile and is active in patients with tumors carrying specific DNA damage response (DDR) alterations.

Objectives and Endpoints:

Objectives	Endpoints
Primary Phase 1b	
To determine the safety and tolerability of niraparib or olaparib in combination with RP-3500 in patients with molecularly selected solid tumors	• Incidence and severity of treatment-emergent adverse events (TEAE), dose-limiting toxicities (DLTs), laboratory assessments, vital signs, electrocardiograms (ECGs), physical examinations, concomitant medications, and exposure
To define the recommended Phase 2 dose (RP2D) of RP-3500 in combination with niraparib or olaparib in patients with molecularly selected solid tumors	• Frequency of DLTs at each dose level during the DLT observation period • RP2D: incidence and severity of treatment-emergent adverse events
[redacted]	
[redacted]	[redacted]

[redacted]	[redacted]
Secondary	
To assess the pharmacokinetic (PK) parameters of RP-3500 in combination with niraparib or olaparib	• Plasma concentrations of RP-3500 and niraparib or olaparib with calculation of maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve 0 to 6 hours post dose (AUC_{0-6}), and other parameters as appropriate
[redacted]	[redacted]

	[redacted]

Overall Study Design

This is a multicenter, open-label Phase 1b/2 study to investigate the safety and efficacy of the combination of the ATRi RP-3500 with the PARPi niraparib or olaparib in patients with advanced solid tumors harboring specific deleterious mutations. Eligible patients should have a specific tumor mutation profile that was demonstrated preclinically to increase sensitivity to the combination agents. The study is designed to determine if a reduced exposure to the combination remains well tolerated and results in significant anti-tumor efficacy to warrant further assessment.

[redacted]

Approximately 160 patients will be enrolled for the dose finding phase (Phase 1b). This includes at least 100 efficacy evaluable patients [redacted] in backfill cohorts. [redacted]

Backfill cohorts (up to 8 patients each) may be employed based on agreement with the Study (Safety) Steering Committee (SSC) to enable an earlier and better understanding of the variability in drug-related toxicity, clinical benefit, or PK. The objective of 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.

The criteria that will be used to trigger enrollment in backfill cohorts is as follows:

- If heterogeneous responses are observed at pharmacologically relevant doses in particular tumor types/genotypes, evaluation of additional patients with a specific genotype tumor type/genotype may be required in order to assess the impact of such variables on response. For instance, differential responses may be observed in the setting of monoallelic vs biallelic alterations or in the setting of reversion mutations.
- If insufficient PK and/or PD data is collected (eg, due to missing assessments/poor sample quality) and/or the variability within the dataset is greater than anticipated, additional patients may be enrolled in backfill cohorts in order to satisfy the protocol objectives.

If new, unexpected (off-target) toxicities are observed or if there are toxicities that appear to be enriched or of higher severity within specific contexts (eg, somatic vs germline mutant patients) then additional patients may be enrolled in backfill cohorts in order to better understand the causality and frequency.

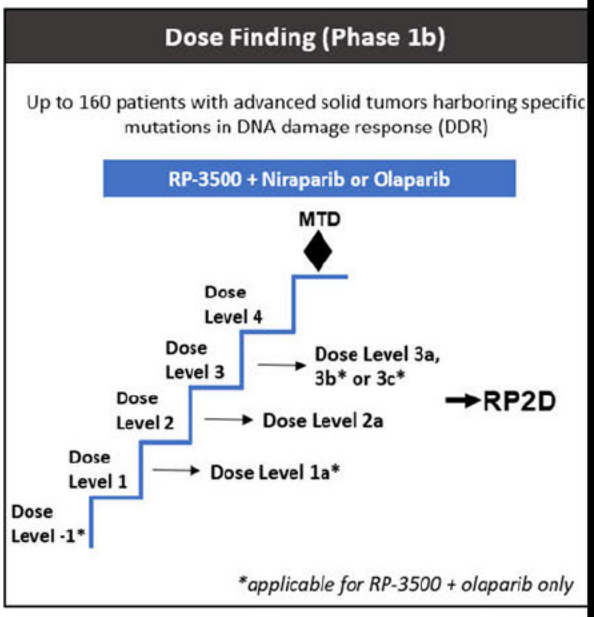
Patients will be enrolled based on local tumor mutation data generated in a College of Pathology (CAP)/Clinical Laboratory Improvement Amendments (CLIA) certified lab (International Organization for Standardization [ISO] or equivalent) and collected following center specific institutional guidelines. Sponsor-approved local next-generation sequencing (NGS) tests include Guardant360®, Caris, Foundation Medicine F1, MSK IMPACT, MSK ACCESS, Oncomine™ V3, Qiagen Comprehensive, Tempus xF/xT, OncoPanel, or other validated platforms. Germline test results will be accepted from Ambry, Invitae, Myriad, or other tests approved by the sponsor. Plasma or tumor tissue NGS results are accepted for all genes. However, for ATM specifically, liquid biopsy is only acceptable with a variant allele frequency (VAF) >25% to eliminate or reduce enrollment through clonal hematopoiesis of indeterminate potential or hematopoiesis of indeterminate significance (CHIP).

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) 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.

The local NGS data will define the biomarker status for patient enrollment. Subsequently, the sponsor will independently confirm the local test results with the centralized NGS assays run in a CAP/CLIA accredited laboratory.

Continuous safety monitoring during the study will allow assessment of toxicity patterns. It is possible that one of the RP-3500 and PARPi combinations will be preferentially tolerated in which case the study will continue with only the PARPi arm that has a better safety profile, after at least 12 patients are evaluated at the RP2D for both PARPi. [redacted]

Study Schema:



[redacted]

Dose Finding Study

The study will begin with accelerated titration by enrolling 1 patient at Dose Level 1 in each arm (RP-3500 in combination with niraparib or olaparib), to minimize the exposure of patients to sub-therapeutic doses. RP-3500 and the PARPi will be administered together weekly, following a concomitant 3 consecutive days on and 4 consecutive days off dosing schedule (3/4 schedule) in 21-day cycles. Administration of RP-3500 and the PARPi may follow an intermittent weekly schedule (eg, 2 weeks on/1 week off, 1 week on/1 week off, 1 week on/2 weeks off) with a cycle length of 21 or 28 days. Niraparib or olaparib administered in combination with RP-3500 may also follow a 2 consecutive days on and 5 consecutive days off dosing schedule (2/5 schedule). Patient enrollment to receive RP-3500 in combination with niraparib or olaparib will be guided by the SSC.

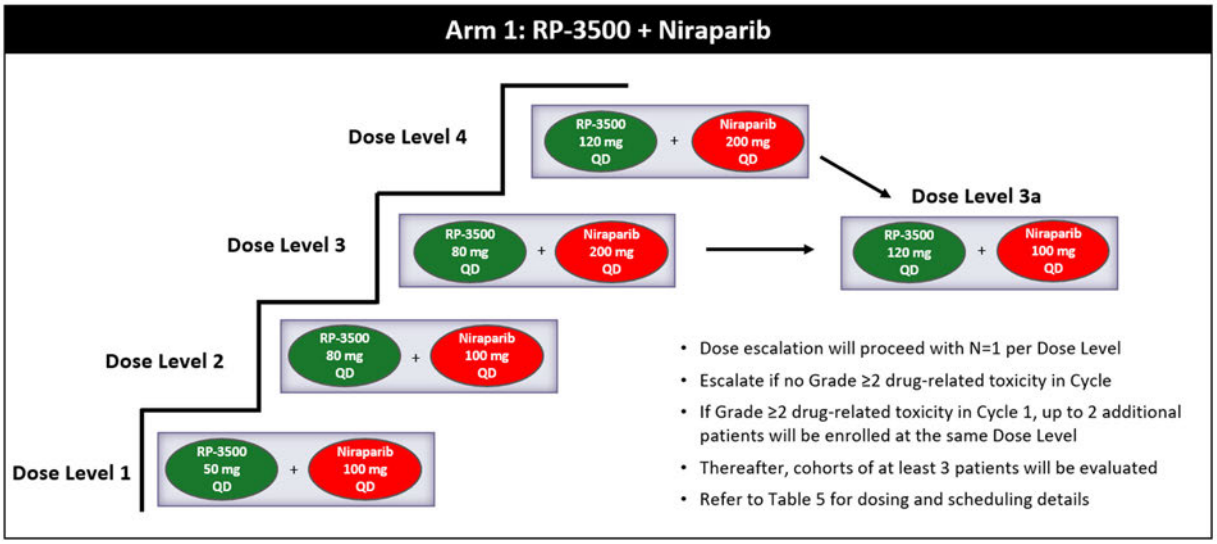
In the absence of Grade ≥2 drug-related toxicity in Cycle 1, dose escalation will progress to the next dose level, with a cohort size of 1 (Dose Level Table and Dose Finding Schema). If Grade ≥2 drug-related toxicity is observed at any time during Cycle 1, up to 2 additional evaluable patients will be enrolled at that dose level to further assess safety and tolerability. Cohorts of at least 3 patients will be evaluated thereafter.

The starting doses will be RP-3500 50 mg orally (PO) once daily (QD) plus niraparib 100 mg PO QD or olaparib 150 mg PO BID. Olaparib may be administered QD as long as the total daily dose does not exceed the BID dose for the respective dose level. All drugs will be given on Days 1-3, 8-10, and 15-17 of each 21-day cycle for the 3 weeks on 3/4 dosing schedule; on Days 1-2, 8-9, and 15-16 of each 21-day cycle for the 3 weeks on 2/5 dosing schedule; on Days 1-2 and 8-9 of each 21-day cycle for the 2 weeks on/1 week off 2/5 dosing schedule; on Days 1-3 of each 21-day cycle for the 1 week on/2 weeks off 3/4 dosing schedule; or on Days 1-3 and 15-17 of each 28-day schedule for the 1 week on/1 week off 3/4 dosing schedule. Dosing and scheduling details are presented in the tables below.

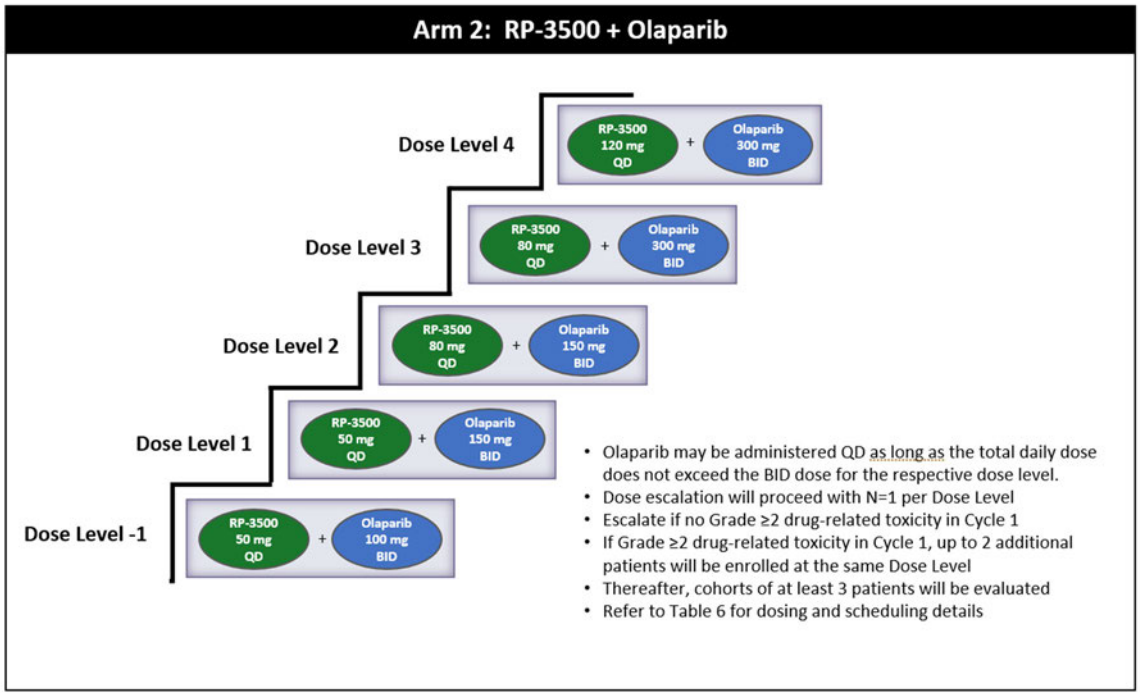
RP-3500 as monotherapy is currently being evaluated in a Phase 1 first-in-human study (NCT04497116). A RP2D dose for RP-3500 was established at 160 mg 3 days on/4 days off administered weekly, with dose de-escalation schedules proposed as 120 mg on the same schedule of 160 mg administered 3 days on/4 days off and 2 weeks on/1 week off. As of 12 July 2021, 85 patients have been accrued into the study, and 79 patients have been treated with monotherapy of RP-3500 in doses ranging from 5 mg to 160 mg QD and 40 mg to 80 mg BID, given on a 5 consecutive days on/2 consecutive days off or 3 days on/4 days off schedule. Further updates to the clinical safety data in the RP-3500-01 study can be found in the Investigator Brochure (IB).

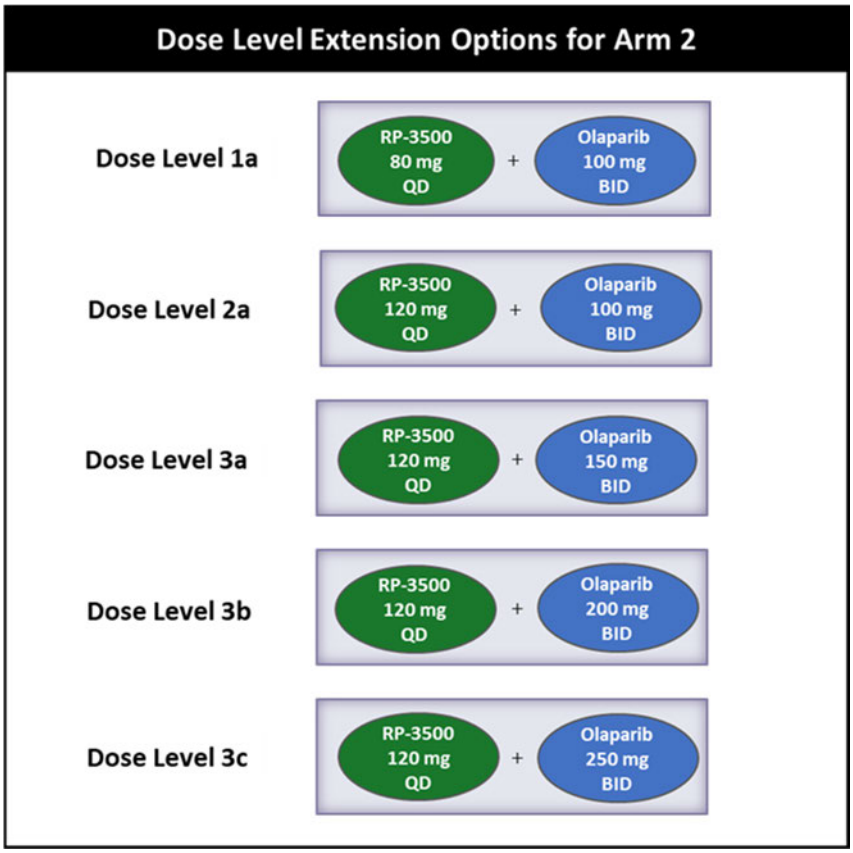
The initial dose of 50 mg QD for RP-3500 for 3 days (3/4 dosing schedule) was chosen based on the observed tolerability of RP-3500 monotherapy given at 160 mg QD on a 3/4 dosing schedule.

Phase 1 Dose Finding Study Schema For Arm 1



Phase 1 Dose Finding Study Schema For Arm 2





In the absence of toxicity, dose escalation will follow Dose Levels Tables below as agreed by SSC. Niraparib and olaparib escalations will progress independently.

Phase 1 Dose Levels and Schedules for RP-3500 + Niraparib (Arm 1)

Dose Level	21-Day Cycles				28-Day Cycle
	Schedule: 3 weeks on Dosing: 3 days on/4 days off	Schedule: 3 weeks on Dosing: 2 days on/5 days off	Schedule: 2 weeks on/1 week off Dosing: 2 days on/5 days off	Schedule: 1 week on/2 weeks off Dosing: 3 days on/4 days off	Schedule: 1 week on/1 week off Dosing: 3 days on/4 days off
1	RP-3500 50 mg QD Niraparib 100 mg QD	RP-3500 50 mg QD Niraparib 100 mg QD	RP-3500 50 mg QD Niraparib 100 mg QD	RP-3500 50 mg QD Niraparib 100 mg QD	RP-3500 50 mg QD Niraparib 100 mg QD
2	RP-3500 80 mg QD Niraparib 100 mg QD	RP-3500 80 mg QD Niraparib 100 mg QD	RP-3500 80 mg QD Niraparib 100 mg QD	RP-3500 80 mg QD Niraparib 100 mg QD	RP-3500 80 mg QD Niraparib 100 mg QD

3	RP-3500 80 mg QD Niraparib 200 mg QD	RP-3500 80 mg QD Niraparib 200 mg QD	RP-3500 80 mg QD Niraparib 200 mg QD	RP-3500 80 mg QD Niraparib 200 mg QD	RP-3500 80 mg QD Niraparib 200 mg QD
3a	RP-3500 120 mg QD Niraparib 100 mg QD	RP-3500 120 mg QD Niraparib 100 mg QD	RP-3500 120 mg QD Niraparib 100 mg QD	RP-3500 120 mg QD Niraparib 100 mg QD	RP-3500 120 mg QD Niraparib 100 mg QD
4	RP-3500 120 mg QD Niraparib 200 mg QD	RP-3500 120 mg QD Niraparib 200 mg QD	RP-3500 120 mg QD Niraparib 200 mg QD	RP-3500 120 mg QD Niraparib 200 mg QD	RP-3500 120 mg QD Niraparib 200 mg QD

Abbreviation: BID = twice daily; QD = once daily

Phase 1 Dose Levels and Schedules for RP-3500 + Olaparib (Arm 2)

	21-Day Cycles				28-Day Cycle
Dose Level	Schedule: 3 weeks on Dosing: 3 days on/4 days off	Schedule: 3 weeks on Dosing: 2 days on/5 days off	Schedule: 2 weeks on/1 week off Dosing: 2 days on/5 days off	Schedule: 1 week on/2 weeks off Dosing: 3 days on/4 days off	Schedule: 1 week on/1 week off Dosing: 3 days on/4 days off
-1	RP-3500 50 mg QD Olaparib 100 mg BID	RP-3500 50 mg QD Olaparib 100 mg BID	RP-3500 50 mg QD Olaparib 100 mg BID	RP-3500 50 mg QD Olaparib 100 mg BID	RP-3500 50 mg QD Olaparib 100 mg BID
1	RP-3500 50 mg QD Olaparib 150 mg BID	RP-3500 50 mg QD Olaparib 150 mg BID	RP-3500 50 mg QD Olaparib 150 mg BID	RP-3500 50 mg QD Olaparib 150 mg BID	RP-3500 50 mg QD Olaparib 150 mg BID
1a	RP-3500 80 mg QD Olaparib 100 mg BID	RP-3500 80 mg QD Olaparib 100 mg BID	RP-3500 80 mg QD Olaparib 100 mg BID	RP-3500 80 mg QD Olaparib 100 mg BID	RP-3500 80 mg QD Olaparib 100 mg BID
2	RP-3500 80 mg QD Olaparib 150 mg BID	RP-3500 80 mg QD Olaparib 150 mg BID	RP-3500 80 mg QD Olaparib 150 mg BID	RP-3500 80 mg QD Olaparib 150 mg BID	RP-3500 80 mg QD Olaparib 150 mg BID
2a	RP-3500 120 mg QD Olaparib 100 mg BID	RP-3500 120 mg QD Olaparib 100 mg BID	RP-3500 120 mg QD Olaparib 100 mg BID	RP-3500 120 mg QD Olaparib 100 mg BID	RP-3500 120 mg QD Olaparib 100 mg BID
3	RP-3500 80 mg QD Olaparib 300 mg BID	RP-3500 80 mg QD Olaparib 300 mg BID	RP-3500 80 mg QD Olaparib 300 mg BID	RP-3500 80 mg QD Olaparib 300 mg BID	RP-3500 80 mg QD Olaparib 300 mg BID

3a	RP-3500 120 mg QD Olaparib 150 mg BID	RP-3500 120 mg QD Olaparib 150 mg BID	RP-3500 120 mg QD Olaparib 150 mg BID	RP-3500 120 mg QD Olaparib 150 mg BID	RP-3500 120 mg QD Olaparib 150 mg BID
3b	RP-3500 120 mg QD Olaparib 200 mg BID	RP-3500 120 mg QD Olaparib 200 mg BID	RP-3500 120 mg QD Olaparib 200 mg BID	RP-3500 120 mg QD Olaparib 200 mg BID	RP-3500 120 mg QD Olaparib 200 mg BID
3c	RP-3500 120 mg QD Olaparib 250 mg BID	RP-3500 120 mg QD Olaparib 250 mg BID	RP-3500 120 mg QD Olaparib 250 mg BID	RP-3500 120 mg QD Olaparib 250 mg BID	RP-3500 120 mg QD Olaparib 250 mg BID
4	RP-3500 120 mg QD Olaparib 300 mg BID	RP-3500 120 mg QD Olaparib 300 mg BID	RP-3500 120 mg QD Olaparib 300 mg BID	RP-3500 120 mg QD Olaparib 300 mg BID	RP-3500 120 mg QD Olaparib 300 mg BID

Abbreviation: BID = twice daily; QD = once daily
Olaparib may be administered QD as long as the total daily dose does not exceed the BID dose for the respective dose level.

If no DLT is observed at the highest proposed doses (Dose Level 4), 1 additional escalation of RP-3500 will be permitted by up to 50% of the last daily dose given.

Initially, dose finding will start with RP-3500 QD administration but a BID schedule could be explored if significant toxicity is observed.

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

Dose-Limiting Toxicity Criteria:

Toxicity will be assessed with the guidance of 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, meets the pre-defined criteria for DLT, 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 adverse events (AEs):

- Grade 4 neutropenia lasting at least 7 days
- Febrile neutropenia (defined as absolute neutrophil count <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

The use of transfusions and hematopoietic growth factors, including thrombopoietin analogues, will be part of the DLT definition if such intervention is required.

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 laboratory abnormality that are not considered clinically relevant in the opinion of the investigator, or respond to medical intervention*
  - *Grade 3 fatigue with duration of <7 days and resolved to Grade ≤2, unless repeatedly observed and considered drug related upon SSC discussion*
  - *Grade 3 nausea/vomiting/diarrhea unless refractory to supportive care that lasts <3 days*

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 at any time during the initial cycle of the study.

Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 80% of planned total doses of study treatment, completes all required safety evaluations per the Schedule of Assessments, and is observed within 21 or 28 days following the first dose of study treatment.

[redacted]

[redacted]

General Study Conduct:

The study will consist of a patient Pre-screening Period (within 6 months from time of screening/main informed consent form [ICF] signature, to confirm eligibility of genetic mutation), Screening Period (Day -28 to Day -1, to determine overall study eligibility per inclusion/exclusion criteria), Treatment Period (21-day cycles or 28-day cycles), and 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 the patient discontinued due to a treatment-related toxicity). If a patient is removed from the study due to a treatment-related toxicity, an additional safety follow-up visit will occur within 30 days (+14 days) after the last dose of study drug. Survival Follow-up will be conducted every 3 months ± 2 weeks until the end of the study unless the patient withdraws consent to the study or the study is terminated prior to the 12-month follow-up period.

Study Procedures:

Study procedures will occur as outlined in the Schedule of Assessments (SOA). Safety and tolerability will be followed by the Medical Monitor and evaluated by the SSC throughout the study. Assessments conducted throughout the treatment period will include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment discontinuations or dose reductions due to AEs, DLTs, changes in Eastern Cooperative Oncology Group (ECOG) performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination (PE), 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. For patients with prostate cancer, radionuclide bone scans will also be required at baseline as per the Prostate Cancer Working Group 3 (PCWG3) criteria (Appendix 3). 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 (Appendix 2), and PCWG3 criteria for patients with prostate cancer (Appendix 3), or Gynecological Cancer Intergroup (GCIG) definitions for response and progression in patients with ovarian cancer (Appendix 4). Response will be assessed by the Investigator.

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 will be performed every 9 weeks (±7 days). Per RECIST v1.1, CR or PR should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response but may be done at the next scheduled assessment. 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 ±7 days thereafter).

For patients with prostate cancer and bone lesions at baseline, follow-up radionuclide bone scans will be required at the same frequency as the RECIST assessments for assessment of progression of bone disease as per PCWG3. For PD as defined by PCWG3 as a result of new bone lesions, progression should be confirmed on a subsequent bone scan. For patients with prostate cancer and non-measurable disease only, bone scans should be performed at baseline and as clinically indicated.

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 study consent, 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.

Laboratory Assessments:

Blood samples will be collected throughout the study to closely monitor safety parameters and characterize the pharmacokinetic (PK) profile of RP-3500 and niraparib or olaparib when administered in combination. Patients with cancers being monitored by specific circulating tumor biomarkers, including but not limited to cancer antigen 125 (CA-125) or prostate-specific antigen (PSA), will continue to have these laboratory assessments performed during Screening or prior to first dose on Cycle 1 Day 1 and at least once per cycle while on study and at EOT. For all patients with prostate cancer, 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 criteria (Appendix 3). For patients with ovarian cancer, CA-125 measurement will also be mandatory at baseline and on Day 1 of each cycle (through and including EOT) as part of the evaluation of response per the GCIG criteria (Appendix 4).

Blood samples for the analysis of ctDNA will be obtained pre-treatment, throughout treatment, and at EOT.

Tumor Tissue:

All patients must provide a tumor tissue sample either archival or fresh biopsy during the Screening Period. It is recommended that the tumor tissue sample has been collected within 24 months of signing the screening/main informed consent. The most recent archival tumor tissue sample available is preferred and the tumor cell content must be confirmed by center pathologist at >30% prior to shipping. The tumor sample, along with the confirmation of cellularity, must be shipped to the central laboratory prior to Cycle 1/Day 1+7 days. If available, the sponsor will also request archival material from the primary tumor- this is optional and not required for enrollment. 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. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample. 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. An optional tumor biopsy will also be requested at disease progression.

Eligibility:

Inclusion Criteria:

Patients must meet all of the inclusion criteria listed below to be eligible for participation in the study:

1. Written informed consent, according to local guidelines, signed and dated by the participating patient or legal guardian prior to the performance of any study-specific procedures, sampling, or analyses. Patients with impaired decision-making capacity must have a close caregiver or legally authorized representative (LAR) present.
2. Male or female patient ≥18 years of age at the time of signature of the ICF.
3. Ability to comply with the protocol and study procedures detailed in the Schedule of Assessments.
4. Patient must have locally advanced or metastatic solid tumor that has progressed or was non-responsive or intolerant to available therapies and for which no standard or available curative therapy exists, or in the opinion of the investigator, is not a candidate for, or would be unlikely to tolerate or derive significant clinical benefit from, appropriate standard of care therapy, or if the patient declines standard-of-care therapy. Documented counselling by center investigator on benefits/risks of standard-of-care therapy is required for enrolled patients who decline standard-of-care therapy.
5. ECOG performance status of 0 or 1.
6. Patients must have evaluable disease per RECIST v1.1. For patients with prostate cancer or ovarian cancer that have non-measurable disease, PCWG3 criteria (radionuclide bone scan and PSA, refer to Appendix 3) or GCIG criteria (CA-125, refer to Appendix 4) will be used respectively to assess anti-tumor activity.
7. Tumor, germline, or plasma DNA analysis for all patients must be performed in a CLIA accredited laboratory (or equivalent), confirmed by PODS and must meet one of the following biomarker requirements:
    a. Deleterious *ATM, CDK12, PALB2, RAD51B, RAD51C,* or *RAD51D* mutation or other genes decided upon between the sponsor and investigators. *Justification and agreement between investigator and sponsor will be documented.*
    b. ATM confirmed by liquid biopsy: liquid biopsy results will only be accepted for patients with ATM, if the ATM VAF is > 25%. However, an ATM VAF of < 25% can

be accepted if the ctDNA test is performed in parallel with testing of a matched whole blood sample to confirm that the alteration is tumor derived.

c. Deleterious *BRCA1* or *BRCA2* mutation. Patients must have the following:

i. Presence of a deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutation.
ii. For patients with ovarian or pancreatic cancer previously treated with platinum-based therapy, platinum sensitivity as measured by at least 6 months of platinum-free interval (PFI) must be documented. *PFI can occur at any time of the disease course, including immediately prior to trial enrollment.*

d. Loss of tumor ribonuclease H2 (*RNASEH2)* by one of the following methods:

i. *RNASEH2* immunohistochemistry (IHC) loss
ii. *RNASEH2A* or *RNASEH2B* homozygous loss determined by NGS
iii. *RNASEH2A* loss of heterozygosity (LOH) or *RNASEH2B* LOH and IHC loss

Note: The sponsor will provide a separate guidance document for molecular eligibility.

8. Provision of archival tumor tissue sample (or if adequate tumor tissue is not available, provision of a fresh biopsy if there is a lesion that can be safely biopsied). Sample must be shipped to the sponsor's central laboratory by Cycle 1/Day 1+7 days. It is recommended that the tumor tissue sample has been collected within 24 months of signing the screening/main informed consent. If a fresh biopsy was provided during pre-screening, then a biopsy during screening is not required. Bone tissue is not acceptable for tumor tissue submission because bone biopsies require a decalcification step that will interfere with downstream processing of the sample. 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.
9. Life expectancy ≥12 weeks after the start of the treatment according to the investigator's judgment.
10. Acceptable hematologic function at Screening:
    a. No red blood cell or platelet transfusions or growth factors within 14 days of the first dose and stable platelet/hemoglobin levels, based on investigator judgement
    b. Absolute neutrophil count ≥1500/µL
    c. Hemoglobin ≥10.0 g/dL
    d. Platelets ≥120,000/µL
11. Acceptable organ function at Screening, as evidenced by the following laboratory data:
    a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 × upper limit of normal (ULN).
    b. Either glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, or calculated creatinine clearance (CrCl) ≥60 mL/min using Cockcroft-Gault equation (or by 24-hour urine collection).
    c. Total bilirubin ≤1.5 × ULN or <3.0 × ULN if known Gilbert's disease.
12. Negative pregnancy test (serum) for women of childbearing potential (WOCBP) at Screening.
    a. WOCBP is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP and their partners must agree to use a

highly effective form of contraception as detailed in Appendix 1 throughout their participation during study treatment and for 6 months after the last dose of study drugs.

b. 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 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.

c. Female patients must refrain from donating eggs during their participation in the study and for 6 months following last dose of study drug.

13. 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 during their participation in the study and for 6 months following last dose of 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.
14. Ability to swallow and retain oral medications.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Tumors that have a deleterious mutation in *BRCA1* or *BRCA2* gene that were treated with PARPi and progressed during treatment without any evidence of prior response are non-eligible for the study. Patients who had stable disease (SD), partial response (PR) or complete response (CR) evaluation while being treated with PARPi treatment and/or subsequently progressed, are still considered eligible for the study.
2. Prior therapy with an ATRi or DNA-dependent protein kinase (DNA-PK) inhibitor.
3. Chemotherapy, small molecule anticancer or biologic anticancer therapy given within 10 days or 5 half-lives (whichever is shorter) prior to the first dose of study treatment.
4. Use of radiotherapy (except for palliative reasons) within 7 days prior to study treatment initiation.
5. No other anticancer therapy (chemotherapy, immunotherapy, hormonal anticancer therapy, biological therapy, lanreotide/octreotide for NET/NECs, or other novel agent) is to be permitted while the patient is receiving study treatment. For patients with breast or prostate cancer continuation of long-term luteinizing hormone-releasing hormone (LHRH), gonadotrophin releasing hormone (GnRH), or previously prescribed receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor are allowed if these medications were prescribed for at least 4 months before study entry. Bisphosphonates are allowed if prescribed at least 28 days prior to enrollment.
6. Major surgical procedures ≤28 days prior to study treatment initiation, or minor surgical procedures ≤7 days prior to study treatment initiation. Patients must have recovered from any of the effects of any major surgery. No waiting period is required following implanted/port-a-cath placement or other central venous access placement.

7. Persistent Grade >1 toxicity from prior cancer therapy (except alopecia, anorexia, or toxicity that is stable and poses no significant risk to the participant). Grade 2 peripheral neuropathy after documented treatment with taxanes and/or platinum-based therapy is allowed.
8. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, or non-malignant systemic disease. Examples include but are not limited to uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or extensive interstitial bilateral lung disease on high resolution computed tomography scan.
9. Moderate or severe hepatic impairment (ie, Child-Pugh class B or C).
10. Known malignant central nervous system disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or hemorrhage for at least 4 weeks after treatment (including brain radiotherapy). Must be off any systemic corticosteroids for the treatment of symptomatic brain metastases for at least 14 days prior to enrollment, however a short course of treatment with steroids during palliative radiation is allowed.
11. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg; diastolic BP ≥100 mmHg) despite adequate treatment prior to first dose of treatment.
12. Patients with either previous or current myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or features suggestive of MDS/AML.
13. Any of the following cardiac diseases currently or within the last 3 months prior to study treatment initiation as defined by the New York Heart Association ≥Class 2:
    a. Unstable angina pectoris
    b. Congestive heart failure
    c. Acute myocardial infarction
    d. Conduction abnormality not controlled with pacemaker or medication
    e. Significant ventricular or supraventricular arrhythmias

    (NOTE: Patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible.)
14. History of Torsades de pointes (TdP) unless all risk factors that contributed to TdP have been corrected.
15. Mean resting QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec/male patients and >470 msec/female patients (as calculated per institutional standards) obtained from triplicate ECG ≥1 minute apart at study entry. Please review Appendix 6 for reference of concomitant medications associated with a risk of QTc interval prolongation.
16. Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus, 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 the sponsor medical monitor and will be based on current and past CD4 and T-cell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment.
17. Presence of other known active invasive cancers.
18. Female patients must refrain from nursing/breastfeeding during their participation in the study and for 30 days following last dose of study drug.

19. Patients who are receiving moderate or strong cytochrome P450 (CYP) 3A 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. Please review Appendix 7.
20. Any known hypersensitivity or contraindication to the components of the study drugs RP-3500, niraparib, and olaparib.
21. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the study protocol and/or follow-up procedures outlined in the protocol.

Investigational Product, Dosage, and Mode of Administration:

All drugs will be self-administered and taken together according to the following schedules:

- **3 weeks on - 3 days on/4 days off schedule**
  - Taken on Days 1-3, 8-10, and 15-17 of each 21-day cycle
- **3 weeks on - 2 days on/5 days off schedule**
  - Taken on Days 1-2, 8-9, and 15-16 of each 21-day cycle
- **2 weeks on/1 week off – 2 days on/5 days off**
  - Taken on Days 1-2 and 8-9 of each 21-day cycle
- **1 week on/2 weeks off - 3 days on/4 days off**
  - Taken on Days 1-3 of each 21-day cycle
- **1 week on/1 week off - 3 days on/4 days off**
  - Taken on Days 1-3 and 15-17 of each 28-day cycle

RP-3500 and niraparib will be administered QD, whereas olaparib will be administered BID. Olaparib may be administered QD as long as the total daily dose does not exceed the BID dose for the respective dose level.

Patients should take their drugs with 240 mL (~8 oz) of water and take their morning (RP-3500 and either niraparib or olaparib) and evening dose (olaparib BID only) approximately 12 hours apart. Patients will be instructed to take their drugs at approximately the same time each day. Patients must swallow and not chew all capsules/tablets.

The starting dose levels for the two treatment combinations will be RP-3500 50 mg PO QD plus niraparib 100 mg PO QD or olaparib 150 mg PO BID. Olaparib may be administered QD as long as the total daily dose does not exceed the BID dose. A BID dosing schedule for RP-3500 may be explored if significant toxicity is observed with QD dosing.

RP-3500 will be supplied as immediate-release solid dosage form for oral administration. Niraparib will be supplied as immediate-release hard capsules for oral administration of 100 mg strength. Olaparib will be supplied as immediate-release tablets for oral administration in 100 mg or 150 mg strengths.

Dose interruptions and dose reduction to manage toxicities are allowed and will be carefully monitored by the SSC.

Duration of Treatment:

Treatment will continue until disease progression by RECIST v1.1 criteria, and PCWG3 or GCIG criteria (for patients with prostate and ovarian cancer), intolerability to study drug, risk to patient as

determined by the investigator and/or sponsor, consent withdrawal, start of a non-study anticancer treatment, protocol noncompliance, pregnancy, or death. After treatment discontinuation, patients will be followed for survival. Survival Follow-Up assessments will be done via telephone (or standard method used by participating centers as agreed upon by the sponsor), every 3 months (± 2 weeks) until the end of the study unless the patient withdraws consent to the study or the study is terminated prior to the 12-month follow-up period.

Safety:

Non-serious AEs related to study required procedures will be collected and recorded for each patient from the day of signing the written ICF until start of dosing and non-serious AE regardless of causality from start of dosing until 30 days after the last dose of study drug. Unrelated SAEs are required to be captured through 30 days after cessation of study treatment (or until the patient starts a new anticancer therapy prior to the 30 days). Any SAEs that are assessed by the Investigator as related to study treatment should be reported until the end of the survival follow-up period, which is up to 12 months after the last dose of IP or until lost to follow-up, patient withdrawal of consent, or patient death.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the TEAE or SAE has resolved, abnormal laboratory values have normalized, stabilized, or returned to baseline and there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up or has died. Any AE that occurs beyond the reporting period that the investigator assesses as related to RP-3500 and/or niraparib or olaparib should be reported to Repare Therapeutics.

Tolerability and safety will be evaluated by assessment of AEs, TEAEs, SAEs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, chemistry, and urinalysis), ECOG performance status, ECGs, and exposure (including dose interruptions and modification).

Statistical Methods and Considerations:

Detailed methodology for reporting of study data will be documented in the Statistical Analysis Plan (SAP).

Sample Size:

The planned sample size is approximately 160 patients for the dose finding phase (Phase 1b). This includes at least 100 efficacy evaluable patients that will be enrolled in backfill cohorts. [redacted] Depending on the toxicity profile of the combinations and the number of cohorts required to establish the MTD/RP2D, the actual study sample size may be smaller.

Dose Finding-BOIN Design:

The BOIN design with accelerated titration will be employed to find the MTD of each treatment combination independently. The target toxicity rate is 25%. The maximum sample size will be 30 patients per PARPi combination. DLTs occurring within the first cycle will be used for dose finding.

BOIN design uses the following rule, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤0.197 (<20%), escalate the dose to the next higher dose level.
- If the observed DLT rate at the current dose is ≥0.298 (>30%), de-escalate the dose to the next lower dose level.
- Otherwise, stay at the current dose.

For each treatment combination, dose finding starts at Dose Level 1. The steps to implement the BOIN design are described as follows:

1. Perform accelerated titration as follows: treat the first patient at Dose Level 1. If no Grade ≥2 drug-related toxicity is observed, escalate the dose to the next higher level. Continue this one-patient-per-dose dose escalation process until a Grade ≥2 drug-related toxicity is observed during Cycle 1, or the highest dose level is reached, and then treat up to 2 additional patients at that dose level. Hereafter, cohorts of at least 3 patients will be evaluated, as described in Steps 2 and 3.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in the Dose Escalation/De-Escalation Rules Table below.
3. Repeat Step 2 until the maximum sample size of 30 patients is reached within the specific PARPi combination in Phase 1, or if the number of patients treated at the current dose reaches 9 and the decision according to the Dose Escalation/De-Escalation Rules Table (below) is to stay at the current dose or a decision is made by the SSC to stop.

Dose Escalation/De-Escalation Rule for the BOIN Design

	Number of Patients Treated at Current Dose								
	1	2	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	0	0	0	0	1	1	1	1
Stay at current dose	NA	NA	NA	1	1	NA	2	2	2
Deescalate if # of DLT ≥	1	1	1	2	2	2	3	3	3
Eliminate if # of DLT ≥	NA	NA	3	3	3	4	4	4	5

Abbreviations: BOIN = Bayesian optimal interval; DLT = dose-limiting toxicity
Note: # of DLT is the number of patients with at least 1 DLT. When none of the actions (ie, escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. "NA" means that a dose cannot be eliminated before treating 3 patients.

After the study is completed, the dose for which the isotonic estimate of the toxicity rate is closest to and no higher than the target toxicity rate of 25% will be selected as the MTD. This computation can be implemented by the shiny app "BOIN" available at http://www.trialdesign.org. The RP2D for each combination will be based on discussion between the investigators and the sponsor and will be either the established MTD or a dose lower than MTD based on the totality of the safety and tolerability.

In the event that operational/practical circumstances result in an over-enrollment (ie, n>3) or under-enrollment (ie, n=2) for a BOIN cohort, the next dose level decision would be based on the actual number of patients exposed in the cohort and the BOIN criteria.

The recommended Phase 2 dose maybe lower than the MTD.

Efficacy Analysis:

After the MTDs/RP2Ds of the treatment combinations are established from dose escalation and backfill cohorts, [redacted] at the RP2D dose ([redacted]

[redacted] at least 6 patients from Phase 1b at the RP2D) will be analyzed to further evaluate the safety/tolerability profile, early efficacy signals and perform correlative pharmacokinetic/pharmacodynamic (PK/PD) studies to explore potential predictive biomarkers of response (ie, ATM mutation/loss, PARPi exposure in *BRCA1/2* mutant ovarian cancer). This sample size will provide approximately 80% power to test the target response rate of 40% against the null response rate of 20%, at the one-sided alpha of 0.1.

[redacted]

[redacted]

Safety Analysis:

Toxicity will be summarized by grade and type. All AEs will be listed, including the verbatim description and Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC). TEAEs are defined as those occurring after the first dose of study drugs and within 30 days following the cessation of treatment, whether or not they are considered related to the study medication.

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.

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, PEs, and usage of concomitant medications and procedures.

PK Analysis:

PK parameters for RP-3500 and niraparib or olaparib will be calculated using non-compartmental

analysis or modeling methods as well as using a population PK model: area under the concentration-time curve from time 0 to 6 hours post dose (AUC_{0-6}), C_{max}, and time to reach C_{max} (T_{max}).

[redacted]

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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APPENDIX 1. CONTRACEPTIVE GUIDELINES

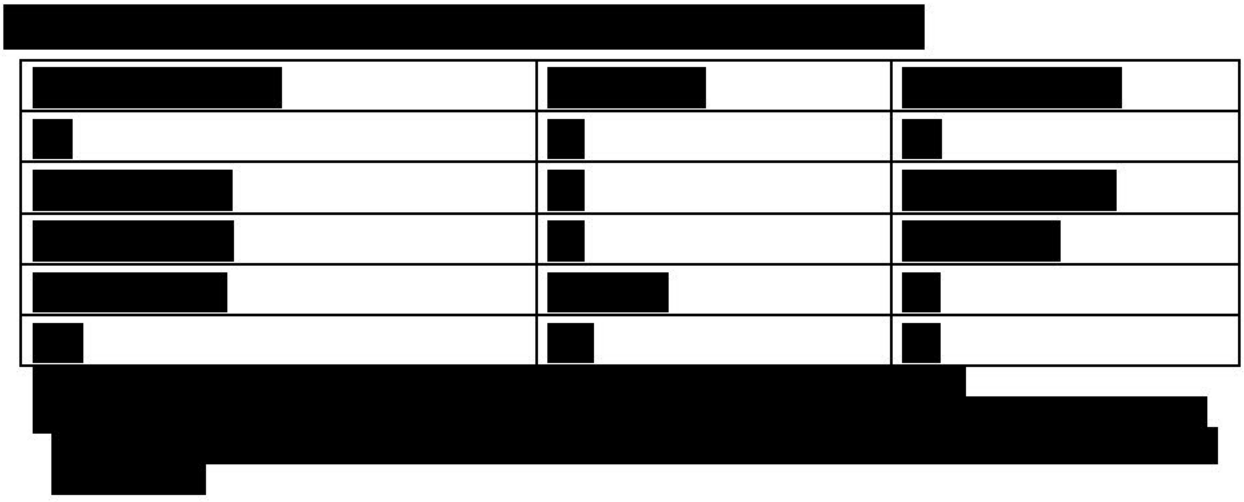
Patients of childbearing potential and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 6 months after the last dose of study drug(s):

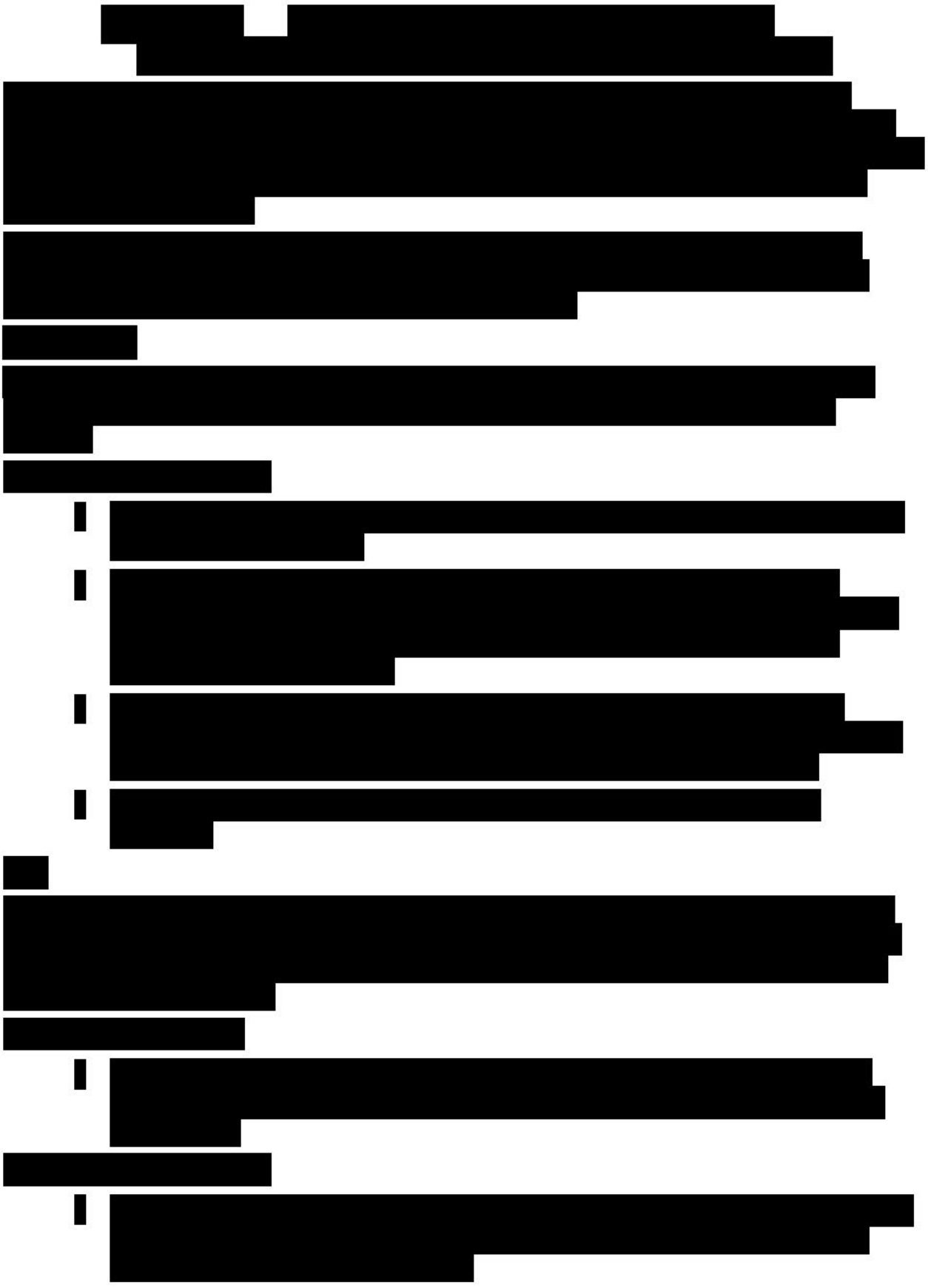
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine 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.

[redacted]

[redacted]





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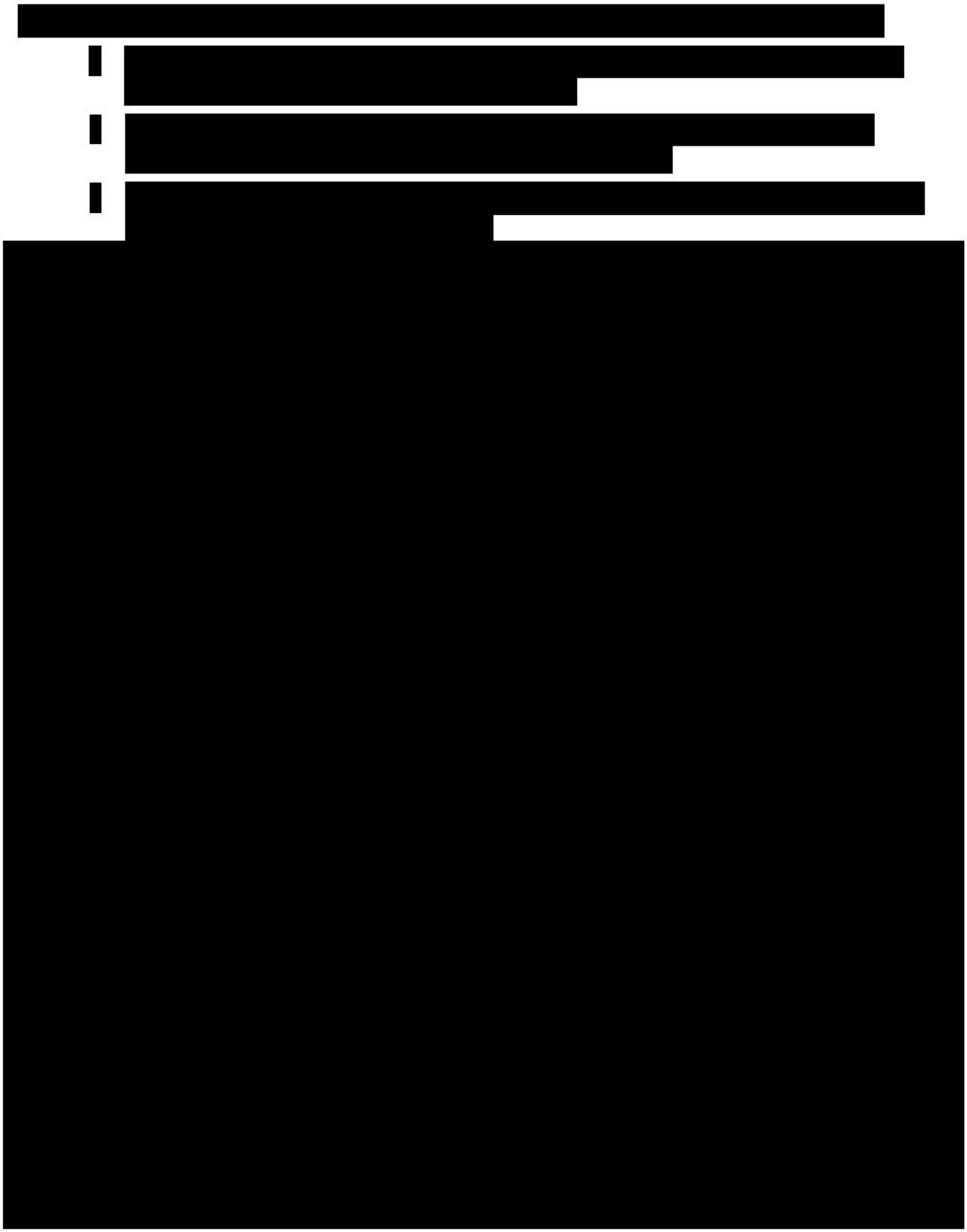

[redacted]

APPENDIX 5. 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 et al., 1982

APPENDIX 6. CONCOMITANT MEDICATIONS ASSOCIATED WITH A RISK OF QTC INTERVAL PROLONGATION AND/OR TORSADES DE POINTES

RP-3500, Olaparib, and niraparib have not demonstrated adverse effects on QT-prolongation in studies to date; however, caution is advised when administering RP-3500, olaparib, and niraparib 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 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 “known risk” should be excluded. Please contact the sponsor 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 7. STRONG CYP3A INHIBITORS AND INDUCERS, P-GP INHIBITORS, AND BCRP INHIBITORS

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

Strong CYP3A Inducers

Inducers	Therapeutic class
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Ivosidenib	Cancer Treatments
Phenytoin	Anticonvulsants

Inducers	Therapeutic class
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