REPARE THERAPEUTICS

Memo To File

To: All RP-3500-01 Clinical Sites

From: [redacted] Executive Vice President, Clinical Development and Medical Affairs

Date: 21 August 2025

RE: RP-3500-01 Study Closure

We are writing to update you on our decision to close the RP-3500-01 study. All patients have completed the study or transitioned on to Single Patient INDs, including to Module 1b NSCLC/ ATM expansion cohort.

On 09 January 2025 Repare Therapeutics announced a re-alignment of resources and a re-prioritization of its clinical portfolio to focus on the continued advancement of its Phase 1 clinical programs, RP-1664 (PLK4 inhibitor) and RP-3467 (Polθ ATPase inhibitor).

The discontinuation of further enrollment and all study related activities in the NSCLC/ATM expansion cohorts is due to the company decision to discontinue further development of camonsertib.

Sincerely

Signed by:
[redacted]
Signing Reason: I approve this document
Signing Time: 22-Aug-2025 | 12:40:25 PM EDT
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Executive Vice President, Clinical Development and Medical Affairs

Repare Therapeutics, Inc

2 SYNOPSIS

Name of Sponsor/Company: Repare Therapeutics	
Name of Investigational Products: Camonsertib (RP-3500)	
Name of Active Ingredients: RP-3500	
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)*	
Study Duration: 39 months	**Phase of Development:** 1/2a
Number of Patients (planned and enrolled): Module 1: Approximately 140 planned and 134 enrolled; Module 2: Up to 191 planned and 20 enrolled. The other modules will be described in subsequent clinical study report(s) (CSR[s]).	
Study Sites: Module 1: 12 study sites (7 in the United States [US], 3 in the United Kingdom [UK], 1 in Canada, and 1 in Denmark. Module 2: 13 study sites (8 in the US, 3 in the UK, 1 in Canada, and 1 in Denmark).	
Publications: Fontana E, Rosen E, Lee EK, Højgaard M, Mettu NB, Lheureux S, et al. ATR inhibitor, camonsertib, dose optimization in patients with biomarker-selected advanced solid tumors (TRESR study). J Natl Cancer Inst. 2024;116(9):1439-49. Pelster M, Silverman IM, Schonhoft JD, Johnson A, Selenica P, Ulanet D, et al. Post-therapy emergence of an NBN reversion mutation in a patient with pancreatic acinar cell carcinoma. NPJ Precis Oncol. 2024;8(1):82. Rosen E, Yap TA, Lee EK, Højgaard M, Mettu NB, Lheureux S, et al. Development of a practical nomogram for personalized anemia management in patients treated with ataxia telangiectasia and Rad3-related (ATR) inhibitor camonsertib. Clin Cancer Res. 2024:30(4): 687–694. Yap TA, Fontana E, Lee EK, Spigel DR, Højgaard M, Lheureux S, et al. Camonsertib in DNA damage response-deficient advanced solid tumors: Phase 1 trial results. Nat Med. 2023 Jun;29(6):1400-1411.	
First Patient First Visit: 22 July 2020 **Last Patient Last Visit:** Study is still ongoing. Data cut-off date for this report is 31 October 2023. As of this date, the last patient dosed with camonsertib monotherapy in Modules 1/2 (on 31 October 2022) was followed for 12 months, the planned follow-up timepoint for writing the CSR as specified in the protocol. Enrollment in Module 1b was subsequently re-initiated in June 2024 to evaluate backfill cohorts of patients with ATM mutated NSCLC.	
Objectives and Endpoints: The purpose of this CSR is to report the study details and results of Modules 1 and 2 (camonsertib monotherapy). Therefore, only the objectives and endpoints for Modules 1 and 2 are presented below. Module 2 was Sponsor prematurely discontinued; therefore, some of the pre-specified study objectives for Module 2 were not assessed.	

Module 1 Primary Objectives:

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

Module 1 Secondary Objectives:

- To assess preliminary anti-tumor activity with camonsertib in patients with eligible advanced solid tumors
- To characterize the pharmacokinetics (PK) profile of camonsertib
- To assess PK parameters of camonsertib monotherapy in fasted and fed states
- To assess the relationship between pharmacodynamic biomarkers and PK of camonsertib 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 camonsertib on QT/corrected QT interval

Module 2 Primary Objective:

- To assess anti-tumor activity of camonsertib 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 (estrogen receptor-positive [ER+]/human epidermal growth factor receptor 2-negative [HER2-]) breast, ampullary, pancreas, prostate, bile duct, and gastroesophageal junction tumors with likely pathogenic/pathogenic germline ataxia telangiectasia-mutated (gATM) mutations
  - **ARM 2**: Leiomyosarcoma tumors with ribonuclease H2 (RNASEH2) loss or deleterious/likely deleterious breast cancer type 2 susceptibility protein (BRCA2) mutations
  - **ARM 3:** Tumors with other ATRi sensitizing biomarkers: ataxia telangectasia-mutated-interacting protein (*ATRIP*), chromosome transmission fidelity protein 8 (*CHTF8*), fizzy-related protein homolog (*FZR1*), meiotic recombination 11 homolog (*MRE11*), nibrin (*NBN*), cell cycle checkpoint protein RAD17 (*RAD17*), cell cycle checkpoint protein RAD50 (*RAD50*), DNA repair protein RAD51 homolog 2/3/4 (*RAD51B/C/D*), protein reversion less

3-like (*REV3L*), SET domain containing 2, histone lysine methyltransferase (*SETD2*), and other genes agreed upon between the Sponsor and Investigator

Module 2 Secondary Objectives:

- To determine safety and tolerability of RP2D and schedule in the biomarker-defined patient subsets
- To assess anti-tumor activity of camonsertib 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 camonsertib

Endpoints

Safety:

- Dose-limiting toxicities (DLTs)
- Incidence of treatment-emergent adverse events (TEAEs), treatment-related AEs (TRAE), TEAEs leading to death, serious adverse events (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 Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT).
- Number and percent of patients who needed transfusion
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), Common Terminology Criteria for Adverse Events (CTCAE) graded laboratory toxicities, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG) parameters, physical examinations (PEs) and usage of concomitant medications and procedures

Efficacy:

- Overall response rate: best response of complete response (CR) or partial response (PR), based on Investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, or response in cancer antigen 125 (CA-125) or prostate-specific antigen (PSA; for patients with prostate cancer without measurable disease) as per Gynecological Cancer Intergroup (GCIG) or Prostate Cancer Working Group 3 (PCWG3).
- Objective response rate (ORR): confirmed best response of CR or PR, based on Investigator's assessment using RECIST v1.1
- Duration of response (DOR): based on Investigator's assessment using RECIST v1.1
- Clinical benefit rate (CBR), based on achieving overall response or remaining on study treatment for at least 16 weeks without evidence of progression
- Progression-free survival time (PFS) and rate of PFS at 6 months, based on Investigator's assessment using RECIST v1.1

Pharmacokinetics:

- 4β-hydroxycholesterol (Module 1c only)
- Total cholesterol (Module 1c only)

Biomarkers:

- pKAP1 and p-gammaH2AX changes in pre- and on-treatment biopsy tissue

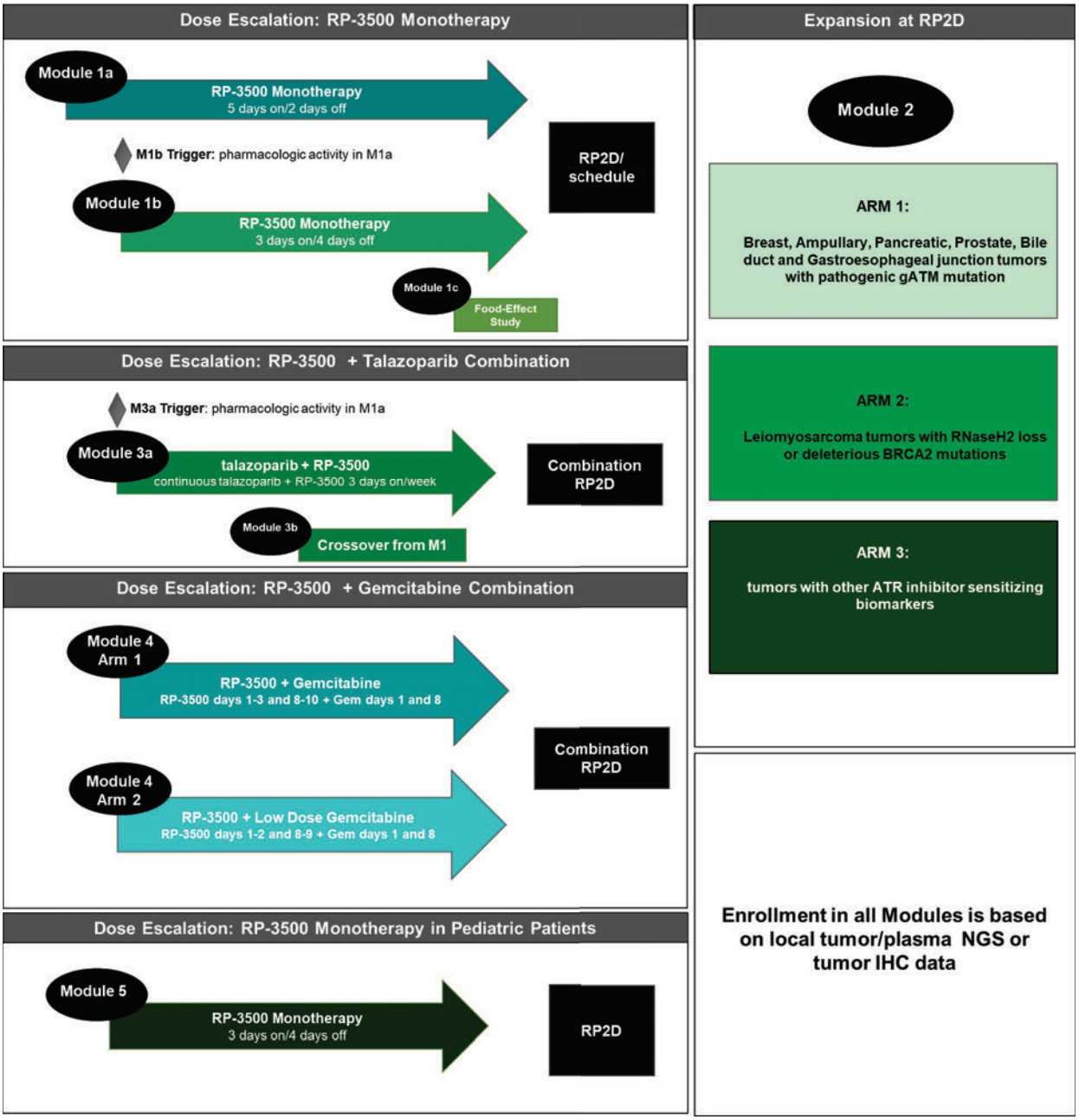
- Baseline genomics profile

Study Design:

This is an ongoing exploratory, modular, Phase 1/2a, first-in-human, multi-center, open-label, non-randomized, dose escalation, and dose-expansion study of camonsertib administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors. There were 5 modules planned in this study. In Modules 1 through 4, approximately 451 patients were expected to be enrolled at approximately 20 sites globally. Enrollment in Module 2 was terminated early per Sponsor decision; Module 5 was closed prior to enrollment of any patients.

The purpose of this CSR is to report the study details and results of Modules 1 and 2. Therefore, only information and data pertaining to Modules 1 and 2 are subsequently described. The other modules will be described in subsequent CSR(s).

Overall Study Design Schema*



Abbreviations: ATR=ataxia telangiectasia-mutated- and rad3-related; BRCA2=breast cancer type 2 susceptibility protein; gATM= germline ataxia telangiectasia-mutated; Gem=gemcitabine; IHC=immunohistochemistry; M=Module; NGS=next-generation sequencing; RnaseH2=ribonuclease H2 subunit B; RP2D=recommended Phase 2 dose; RP-3500=camonsertib.

*Additional schedules may have been tested based on the safety, tolerability, and drug exposure data.

Module 1:

Approximately 140 patients were to be enrolled into Module 1 and to receive camonsertib monotherapy at escalating doses to evaluate the safety, tolerability, PK, and food effect of camonsertib administered using 2 schedules.

Module 1 was composed of 3 sub-modules:

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

Module 2:

Module 2 (up to 191 additional patients were planned to be treated) explored the preliminary efficacy of camonsertib in patients with particular tumors and/or genotypes expected to sensitize ATRi. Camonsertib was administered at a dose level of 160 mg QD on a 3/4 schedule, the preliminary RP2D and schedule for monotherapy that was established in Module 1. Module 2 included 3 arms:

- Arm 1: ER+/HER2- breast, ampullary, pancreas, prostate, bile duct or gastroesophageal junction tumors with likely pathogenic/pathogenic gATM mutations
- Arm 2: Leiomyosarcomas with either 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 InvestigatorEnrollment in Module 2 was terminated early per Sponsor decision.

Inclusion Criteria: 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 informed consent form (ICF).
3. ECOG Performance Status score of 0 or 1.
4. Histologically confirmed solid tumors resistant or refractory to standard treatment and/or patients who were 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 did not apply to patients with rare genomic alterations in Arm 3.
5. Measurable disease as per RECIST v1.1.
    a. Module 1: If the patient had non-measurable disease but had an elevated tumor marker(s) (eg, PSA), patient enrollment may have been discussed between the Investigator and the Sponsor to obtain formal approval.
    b. Module 2: A subset of patients with prostate cancer with non-measurable disease were considered for enrollment if they had elevated PSA levels (>2 ng/mL) evaluable for response per PCWG3.

6. Existing biomarker profile reported from a local test obtained in a College of Pathology (CAP)/Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization (ISO) or equivalent laboratory per institutional guidelines:
   - Module 1:
     - Documented and confirmed by central review of local next-generation sequencing (NGS) reports by the Precision Oncology Decision Support (PODS) Group, deleterious or likely deleterious genomic alterations for at least 1 of the following genes: *ATM*, *ATRIP*, *BRCA1*, *BRCA2*, cyclin-dependent kinase 12 (*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 immunohistochemistry (IHC).
   - Module 2:
     - 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

   Biomarker results were 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 were accepted for ATM.
7. Provision of archival tumor tissue sample (or if adequate archival tumor tissue was not available, provision of a fresh biopsy if there was a lesion that could be safely biopsied). Note: If adequate archived tumor tissue was not available and/or a fresh biopsy could not be safely performed, the patient may still have been 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
    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 were present and thought to be a reason for AST/ALT elevation, in which case they must have been ≤5 × ULN

11. Acceptable hematologic function at Screening:

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

        i. Module 1: 7 days of the first dose of camonsertib

        ii. Module 2: 14 days of first dose of camonsertib

    b. Hemoglobin:

        Module 1: ≥9.5 g/dL

        Module 2: ≥10 g/dL

    c. Absolute neutrophil count (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.

    a. WOCBP was defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP, who were sexually active, and their partners must have agreed to use a highly effective form of contraception as detailed in Appendix 3 of clinical study protocol (CSP) 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).

    b. Women were considered post-menopausal and not of childbearing potential if they had no menses for 12 months without an alternative medical cause or were permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may have been 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 1 FSH measurement was 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 been 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 have followed a contraception method (oral contraceptives allowed) at least as conservative as the Clinical Trial Facilitation Group (CTFG) recommendations (see Appendix 3 of the CSP) during their participation in the study and for 6 months following last dose of study drug. Male patients must have also refrained 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.

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) were allowed if these medications were prescribed for at least 4 months before trial entry.
    - Module 2 only:
        - If patients in Module 2 with ER+/HER2- breast cancer were currently taking anti-estrogen therapy, they could have remained on the same anti-estrogen therapy while on study. If a patient was off anti-estrogen therapy for >28 days, they should not have restarted.
2. History or current condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might have confounded the study results or interfered with the patient's participation for the full duration of the study treatment.
3. Prior therapy with an ATR or deoxyribonucleic acid (DNA)-dependent protein kinase (DNA-PK) inhibitor.
4. Known hypersensitivity to any of the ingredients of camonsertib.
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 have compromised the patient's safety, or interfered with or compromised the integrity of the study outcomes.
6. Uncontrolled, symptomatic brain metastases. Patients with previously treated brain metastases may have participated provided the metastases were stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms were controlled and stable), had no evidence of new or enlarging brain metastases, and were 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 camonsertib.
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 was negative may have been eligible. HIV seropositive patients who were healthy and low risk

for AIDS related outcomes could have been considered eligible. Eligibility criteria for HIV-positive patients was evaluated and discussed with Sponsor's Medical Monitor and was 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 was 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 posed 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 were well-known to prolong the QT interval (see Appendix 4 of the CSP).
14. History of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) diagnosis.
15. Psychological, familial, sociological, or geographical conditions that did not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
16. Patients who were receiving 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.
17. Patients who were pregnant or breastfeeding.

Study Drug(s), Dose and Mode of Administration:

In Module 1, camonsertib was initially administered QD at a starting dose of 5 mg following a 5/2 schedule. Dose escalation decisions were to be informed by the Bayesian optimal design (BOIN) design and protocol-defined dose escalation and de-escalation rules. Camonsertib doses ranged from 5 mg to 160 mg QD and 40 mg to 80 mg twice daily (BID) given on a continuous weekly 5/2 schedule or 3/4 schedule. A 2 weeks on/1 week off schedule (2/1w) was also evaluated at dose levels of 160 and 200 mg QD (3/4 schedule).

In Module 2, camonsertib was administered orally at a dose level of 160 mg QD on a 3/4 schedule, the preliminary RP2D and schedule for monotherapy that was established in Module 1.

Duration of Treatment: Treatment was to continue until disease progression by RECIST v1.1 criteria, intolerability of study drug, Investigator decision, consent withdrawal, start of a non-study anticancer treatment, protocol noncompliance, or death.

Statistical Methods: Detailed methodology for analyses is documented in the Statistical Analysis Plan (SAP).

Analysis Populations:

The following analysis populations were used:

- **DLT Evaluable Population:** patients in Modules 1a or 1b who received at least 80% of planned total doses of camonsertib, completed all required safety evaluations and were observed through the end of Cycle 1, or patients who experienced a DLT. This population was applied to dose escalation decisions in Module 1.
- **Safety Population:** used for the assessment of overall safety and tolerability; all patients who received at least 1 dose of camonsertib.
- **Efficacy Evaluable Population:** all Module 1 and 2 patients who received at least 1 dose of camonsertib at any dose and had at least 1 postbaseline tumor assessment, evaluable for response by RECIST v1.1 and/or GCIG CA-125 criteria or PCWG3 PSA criteria.
- **Primary Efficacy Population:** used for the assessment of efficacy of camonsertib monotherapy; all patients in Module 1 and 2 who received at least 1 dose of camonsertib above 100 mg/day and had at least 1 postbaseline tumor assessment and were evaluable for response by RECIST v1.1 and/or GCIG CA-125 criteria or PCWG3 PSA criteria.
- **Pharmacokinetic Population:** used for the assessment of PK endpoints; all patients who had sufficient PK camonsertib concentration data recorded to derive PK endpoints.

Efficacy Analysis:

The primary efficacy endpoint of overall response rate was 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, CA-125 response based on GCIG criteria, or PSA response based on PCWG3. For a tumor marker responder, there must also have been no evidence of radiologic or clinical progression prior to or within 4 weeks of the initial response.

Safety Analysis:

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 were to be evaluated by dose and schedule for each module and pooled across Modules 1 and 2, where applicable for the Safety Population.

TEAEs were to be further summarized by severity (according to National Cancer Institute [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 use of concomitant medications and procedures were also to be summarized. In addition, DLTs were to be summarized by schedule and Cycle 1 dose level in Module 1 for the DLT Evaluable Population.

Pharmacokinetic Analysis:

PK parameters for camonsertib were to be calculated using non-compartmental analysis or modeling methods as well as using a population PK model: area under the plasma 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_{0-8}), AUC from time 0 to infinite time (AUC_{0-inf}), maximum observed concentration (C_{max}), time to reach C_{max} (T_{max}), and half-life ($t_{1/2}$) were to be calculated along with additional parameters as needed.

The effect of food on exposure to camonsertib was to be assessed by a comparison of geometric mean ratios and the 90% confidence intervals (CIs) of AUC_{0-last}, AUC_{0-inf}, and C_{max}.

Biomarker Analysis:

Assessment of biomarkers may have included but was not limited to gammaH2AX, and KAP1 phosphorylation in pre- and on-treatment biopsies by IHC, pre-treatment genomic assessment, and circulating tumor DNA (ctDNA) dynamics during treatment (Modules 1 and 2). The impact of camonsertib on tumor biology across genotypes was to be evaluated in biopsies collected in Module 1. Biomarker analyses were to be summarized using descriptive statistics. Comparisons of clinical activity between biomarker subpopulations may have been performed.

Results

The data-cutoff date for the data presented is 31 October 2023.

Safety:

Camonsertib was well-tolerated, with a low rate of related SAEs and patient discontinuation due to a TRAE. Anemia was the most common TRAE reported across all dose groups. Grade 3 related anemia rate was lower in patients treated on the 3/4 vs 5/2 schedule (29% vs 56%) and was further improved at the preliminary RP2D of 160 mg QD 3/4 by introducing a 2/1w schedule (11.1% vs 41.8%). Patients on the 2/1w schedule also had a lower rate of RBC transfusions and dose reductions. The most common non-hematologic TRAE across all dose groups was fatigue, which was mostly low grade.

Efficacy:

Overall responses were seen in patients treated with camonsertib doses above 100 mg/day. Responses were observed in patients with diverse tumor types (ovarian, prostate, breast, pancreatic, renal, gastric, head and neck, lung cancer, and melanoma). Of the 133 patients in the Primary Efficacy Population treated with camonsertib doses above 100 mg/day, the overall response rate was 13.5%, the ORR was 8.3%, and CBR was 42.1%. Patients with ovarian cancer had a higher overall response rate (19.2%) and CBR (61.5%) compared to the entire Primary Efficacy Population. Of the 115 efficacy evaluable patients in Modules 1 and 2 treated at potential RP2Ds (120 mg QD 3/4, 160 mg QD 3/4, or 160 mg QD 3/4 on an intermittent weekly 2/1w schedule), the overall response rate was 11.3%, the ORR was 7.0%, and CBR was 38.3%. Efficacy was maintained with adoption of the intermittent weekly 2/1w schedule at the 160 mg QD 3/4 dose level: overall response rate was 19.2%, ORR 15.4%, and CBR 46.2%. A total of 89/115 (77.4%) patients treated at a potential RP2D had PFS events, with a median PFS of 13.6 weeks.

Pharmacokinetics: PK data will be presented upon completion of the study.

Biomarker: Statistically significant increases in γH2AX and pKAP1 were seen (P=0.003, paired Wilcoxon test) and pKAP1 (P<0.001, paired Wilcoxon test), which is consistent with the mechanism of action for camonsertib and confirm biological activity at doses >100 mg/day.

Conclusion:

The observed safety and tolerability of camonsertib was consistent with a highly selective and potent ATRi, with anemia being the most common TRAE. Preliminary anti-tumor activity was observed in heavily pre-treated tumors across a variety of histologic types and gene alterations. Clinical benefit was highest in ovarian cancer.

Based on an improved tolerability profile without any negative impact to efficacy, the 160 mg QD (3/4, 2/1w schedule) dose was selected as the optimized monotherapy regimen for future studies.

The results of this study support the further development of camonsertib, especially in ovarian cancer.

2 SYNOPSIS

Name of Sponsor/Company: Repare Therapeutics

Name of Investigational Products: Camonsertib (RP-3500), talazoparib

Name of Active Ingredients: Camonsertib (RP-3500), talazoparib

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)*

Study Duration: 42 months	**Phase of Development:** 1/2a

Number of Patients (planned and enrolled):

Modules 1 and 2 are described in another report (dated 12 December 2024).

Module 3: Approximately 50 planned and 43 enrolled

The other modules will be described in subsequent clinical study report(s) (CSR[s]).

Study Sites: 12 study sites in the United States, Canada, United Kingdom, Denmark

Publications: None

First Patient First Visit: 10 March 2021

Last Patient Last Visit: 09 May 2024

Objectives and Endpoints:

The purpose of this abbreviated CSR is to report the study details and results of Module 3. Therefore, only the objectives and endpoints for Module 3 are presented below.

Primary Objectives

- To assess the safety and tolerability of camonsertib and talazoparib combination in eligible patients with advanced solid tumors
- To define the maximum tolerated dose (MTD) of camonsertib and talazoparib combination and determine the recommended Phase 2 dose (RP2D) and schedule

Secondary Objectives

- To assess preliminary anti-tumor activity of camonsertib and talazoparib combination in eligible patients with advanced solid tumors
- To assess any pharmacokinetic (PK) interaction of camonsertib and talazoparib when administered in combination
- To determine the PK/pharmacodynamic relationships of camonsertib and talazoparib combination to confirm dose/schedule
- To determine activity of camonsertib and talazoparib combination in patients who progressed after camonsertib alone

Endpoints

Safety:

- Incidence of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs; equivalent to treatment-related TEAEs), TEAEs leading to death, serious adverse events (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 Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT)
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), Common Terminology Criteria for Adverse Events (CTCAE)-graded laboratory toxicities, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG) parameters, physical examinations (PEs) and usage of concomitant medications and procedures

Efficacy:

- Overall response rate: best response of complete response (CR) or partial response (PR), based on Investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, or response in cancer antigen-125 (CA-125) or prostate-specific antigen (PSA) as per Gynecological Cancer Intergroup (GCIG) or Prostate Cancer Working Group 3 (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, based on Investigator's assessment using RECIST v1.1
- Clinical benefit rate (CBR), based on achieving overall response or remaining on study treatment for at least 16 weeks without evidence of progression
- Progression-free survival (PFS) time and rate of PFS at 6 months, based on Investigator's assessment using RECIST v1.1

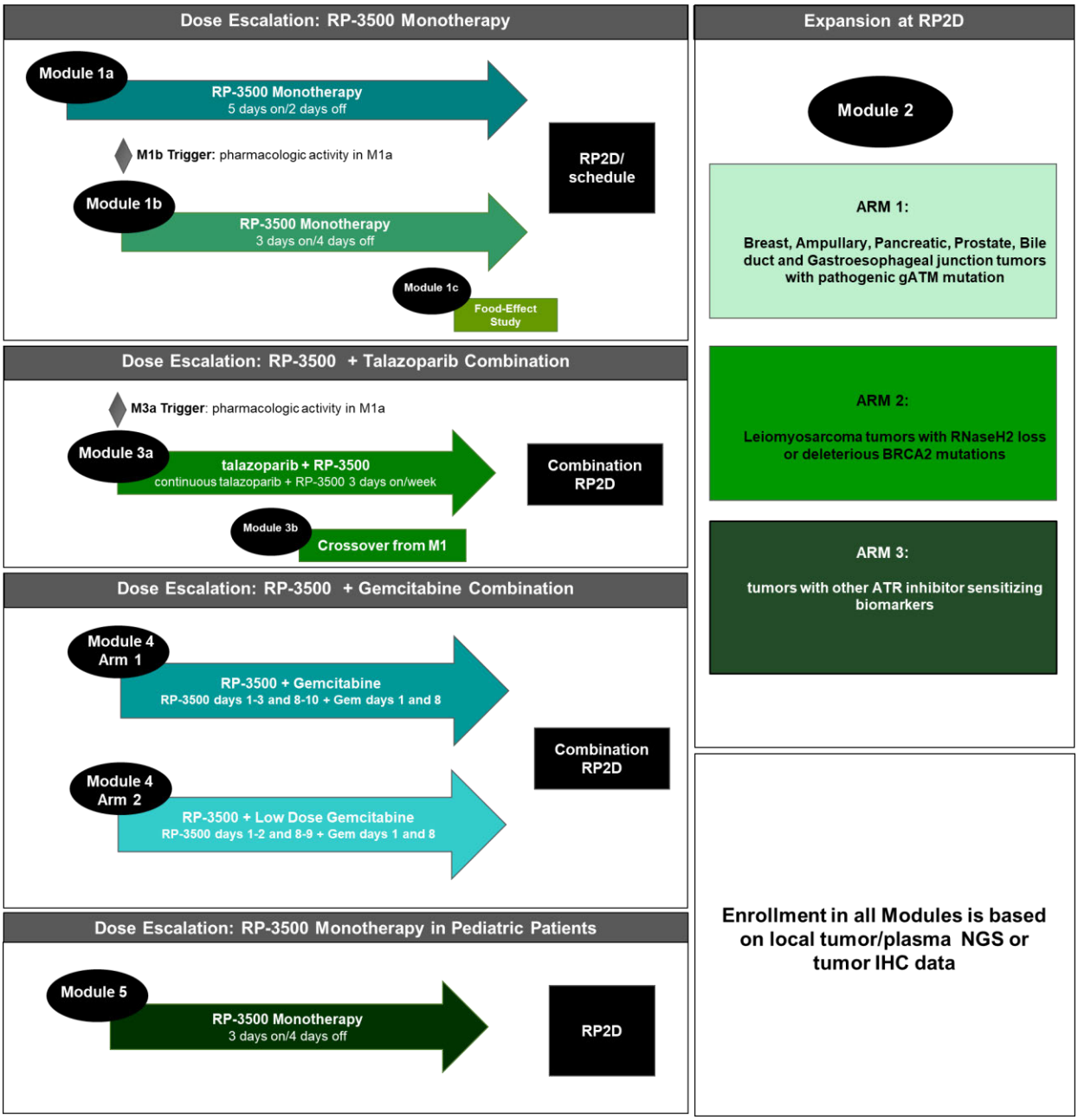
Study Design:

This is an ongoing, exploratory, modular, Phase 1/2a, first-in-human, multi-center, open-label, non-randomized, dose-escalation, and dose-expansion study of camonsertib administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors. There are 5 modules in this study. In Modules 1 through 4, approximately 451 patients are expected to be enrolled at approximately 20 sites globally. Enrollment in Module 2 was terminated early per Sponsor decision; Module 5 was closed prior to enrollment of any patients.

Results from Module 3 of this study are being reported in an abbreviated CSR since further development of camonsertib in combination with talazoparib in patients with advanced solid tumors will no longer be pursued. Subsequently, only information and data pertaining to Module 3 are described herein. Modules 1 and 2 are described in a separate CSR (dated 12 December 2024). The other modules will be described in subsequent reports.

The study consisted 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 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 (every 3 months ± 2 weeks) for 1 year. The treatment period consisted initially of 21-day treatment cycles.

Overall Study Design Schema*



*Additional schedules may have been tested based on the safety, tolerability, and drug exposure data.
Abbreviations: ATR=ataxia telangiectasia-mutated- and rad3-related; BRCA2=breast cancer type 2 susceptibility protein; gATM= germline ataxia telangiectasia-mutated; gem=gemcitabine; IHC=immunohistochemistry; M=Module; NGS=next-generation sequencing; RnaseH2=ribonuclease H2 subunit B; RP2D=recommended Phase 2 dose.

Study procedures were to occur as outlined in the Schedule of Assessments for each module in the clinical study protocol (CSP). Safety and tolerability were to be followed by the Medical Monitor and evaluated by the Safety Review Committee (SRC) throughout the study. Assessments included clinical and laboratory evaluations, information on adverse events (AEs), SAEs, TEAEs, dose-limiting toxicities

(DLTs), PEs, concomitant medications and procedures, vital signs, ECGs, and others.

Module 3:

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

Module 3 was composed of 2 cohorts:

- **Module 3a (Main Cohort):** Patients were to receive talazoparib on Days 1-7 in combination with camonsertib on Days 5, 6, and 7 either weekly or on an intermittent weekly schedule (eg, 1/1w).
- **Module 3b (Crossover Cohort):** Patients whose tumor progressed after treatment in Module 1 (camonsertib monotherapy) had the opportunity to crossover to the highest dose of camonsertib plus talazoparib deemed safe and tolerable in Module 3a, based on eligibility and SRC review.

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 informed consent form.
3. ECOG performance status score of 0 or 1.
4. Histologically confirmed solid tumors resistant or refractory to standard treatment and/or patients who were intolerant to standard therapy.
5. Measurable disease as per RECIST v1.1. Note: If the patient had non-measurable disease but had elevated tumor markers (eg, PSA), patient enrollment could be discussed between the Investigator and the Sponsor to obtain formal approval.
6. Existing biomarker profile reported from a local test obtained in a Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization (ISO) or equivalent laboratory per institutional guidelines:
    a. Documented and confirmed by central review of local next-generation sequencing (NGS) reports by the Precision Oncology Decision Support (PODS) Group, deleterious genomic alterations for at least 1 of the following genes: ataxia telangiectasia-mutated (*ATM*), ataxia telangiectasia-mutated-interacting protein *(ATRIP)*, breast cancer type 1 susceptibility protein (*BRCA1)*, breast cancer type 2 susceptibility protein (*BRCA2)*, cyclin dependent kinase 12 *(CDK12)*, chromosome transmission fidelity protein 8 (*CHTF8)*, Fizzy-related protein homolog *(FZR1)*, meiotic recombination 11 homolog *(MRE11)*, nibrin (*NBN)*, partner and localizer of BRCA2 *(PALB2)*, cell cycle checkpoint protein RAD17 (*RAD17)*, cell cycle checkpoint protein RAD50 (*RAD50)*, DNA repair protein RAD51 homolog 2/3/4 (*RAD51B/C/D)*, protein reversion less 3-like (*REV3L)*, ribonuclease H2 subunit A (*RNAseH2A)*, ribonuclease H2 subunit B (*RNAseH2B)*, SET domain containing 2, histone lysine methyltransferase (*SETD2)*, or other genes decided upon between the Sponsor and Investigators
    b. Or documented complete loss of ATM or ribonuclease H2 (RNAseH2) protein expression by immunohistochemistry (IHC)

7. Provision of archival tumor tissue sample (or if adequate archival tumor tissue was not available, provision of a fresh biopsy if there was a lesion that could be safely biopsied). Note: If adequate archived tumor tissue was not available and/or a fresh biopsy could not be safely performed, the patient could 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
    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 14 days of the first dose of study drugs
    b. Hemoglobin ≥10 g/dL
    c. Absolute neutrophil count ≥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.
    a. WOCBP was defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. WOCBP, who were sexually active, and their partners must have agreed to use a highly effective form of contraception as detailed in Appendix 3 of the CSP throughout their participation during study treatment and for 7 months after the last dose of study drug(s)
    b. Women were considered post-menopausal and not of childbearing potential if they had no menses for 12 months without an alternative medical cause or were permanently sterile. Permanent sterilization methods included hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A high follicle-stimulating hormone (FSH) level in the post-menopausal range could be used to confirm a post-menopausal 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 was 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 have followed a contraception method (oral contraceptives allowed) at least as conservative as the clinical Trial Facilitation Group recommendations (see Appendix 3 of CSP) during their participation in the study and for 6 months following last dose of study drug. Male patients must have also refrained 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.
16. For patients crossing over from Module 1 to Module 3b combination therapy, a biopsy was required at time of progression prior to enrolling into Module 3b. If a biopsy could not be obtained, the Sponsor must have been notified to discuss the possibility of enrolling into Module 3b.

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 or gonadotrophin-releasing hormone was allowed if these medications were prescribed for at least 4 months before trial enrollment.
2. Had a 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 ataxia telangiectasia-mutated- and rad3-related (ATR) or deoxyribonucleic acid (DNA)-dependent protein kinase (DNA-PK) inhibitor.
4. Known hypersensitivity to any of the ingredients of camonsertib.
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 could participate provided the metastases were stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study drug and any neurologic symptoms were controlled and stable), had no evidence of new or enlarging brain metastases, and were 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 camonsertib.
8. Patients with 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 was negative could be eligible. HIV seropositive patients who were healthy and low risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV-positive patients was to be evaluated and discussed with Sponsor's Medical Monitor and was based on current and past cluster of differentiation 4 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 was 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 would pose an increased risk of rhythm abnormalities.
11. QT interval corrected using 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 were well known to prolong the QT interval (Appendix 4 of the CSP).
14. History of myelodysplastic syndrome or acute myeloid leukemia diagnosis.
15. Psychological, familial, sociological, or geographical conditions that did not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
16. Patients who were receiving strong cytochrome P450 (CYP3A) inhibitors or inducers, P-glycoprotein inhibitors and/or breast cancer resistant protein inhibitors within 14 days prior to first dose of study drug (Appendix 5 of the CSP).
17. Known hypersensitivity to any of the ingredients of talazoparib.
18. For patients entering into Module 3b, the following additional exclusion criteria applied:
    a. Rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
    b. Significant, unacceptable, or irreversible toxicities related to the study treatment
    c. Other treatment discontinuation criteria were met
19. Patients who were pregnant or breastfeeding.

Study Drug(s), Dose and Mode of Administration:

Module 3 included administration of both camonsertib and talazoparib.

Talazoparib was self-administered orally QD during each cycle without regard for food, except when taken in combination with camonsertib. The starting dose of talazoparib was 0.5 mg QD.

Camonsertib was self-administered orally BID on Days 5, 6, and 7 of every week with 240 mL (~8 oz) of water. A QD schedule was to be explored pending emerging PK data or if significant toxicity was observed with BID dosing.

As of Protocol Amendment 4, an intermittent dosing schedule involving scheduled weeks off (eg, 1 week on/2 weeks off [1/2w schedule], 1/1w schedule) of both drugs was to be evaluated given that continuous administration of talazoparib in combination with camonsertib was poorly tolerated.

Duration of Treatment: Treatment was to continue until disease progression by RECIST v1.1 criteria, intolerability of study drug, Investigator decision, consent withdrawal, start of a non-study anticancer treatment, protocol noncompliance, or death.

Patients with progressive disease by RECIST v1.1 criteria, who were clinically stable, may have continued treatment if the Investigator deemed that it was in the patient's best interest. The patient was required to provide a signed written consent to continue receiving the study treatment as long as the following criteria were met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention
- No significant, unacceptable, or irreversible toxicities related to the study treatment
- No other treatment discontinuation criteria were met

These patients were categorized as "progressive disease" and treated only if the study drug safety and tolerability was confirmed upon case presentation at the SRC.

Statistical Methods: Detailed methodology for analyses is documented in the Statistical Analysis Plan (SAP).

Analysis Populations:

The following analysis populations were used:

- **DLT Evaluable Population**: patients in Module 3 who received at least 80% of planned total doses of camonsertib and talazoparib, completed all required safety evaluations per Schedule of Assessments and were observed through the end of Cycle 1, or patients who experienced a DLT.
- **Safety Population:** used for the assessment of overall safety and tolerability; consisted of all patients who received at least 1 dose of camonsertib.
- **Efficacy Evaluable Population:** all Module 3 patients who received at least 1 dose of camonsertib, were evaluable for RECIST response or tumor marker response (GCIG criteria for CA-125 or PCWG3 for PSA criteria), had at least 1 post-baseline radiographic tumor assessment or sufficient post-baseline tumor marker assessment meeting GCIG CA-125 or PCWG3 PSA criteria, and without any key eligibility criteria deviation.
- **Pharmacokinetic Population:** used for the assessment of PK endpoints; consisted of all patients who had sufficient PK camonsertib (and talazoparib) concentration data recorded to derive PK endpoints.

Efficacy Analysis:

The primary efficacy endpoint of overall response rate was 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, CA-125 response based on GCIG criteria, or PSA response based on PCWG3. For a tumor marker responder, there must also have been no evidence of radiologic or clinical progression prior to or within 4 weeks of the initial response.

Safety Analysis:

Incidence of TEAEs, TRAEs, 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 were to be evaluated by dose and schedule, where applicable for the Safety Population.

TEAEs were further summarized by severity (according to National Cancer Institute 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 use of concomitant medications and procedures were also to be summarized. In addition, DLTs were to be summarized by Cycle 1 dose level/schedule for the DLT Evaluable Population.

Pharmacokinetic Analysis:

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

Results:

The data cut-off date for the data presented is 09 May 2024.

Safety:

In Module 3a, TRAEs were reported in 83.7% of patients. Anemia was the most common TRAE of any grade (65.1%), and neutropenia was the most common grade ≥3 TRAE (48.8%). Serious TRAEs occurred in 11.6% of patients including in 2/5 patients treated on the continuous weekly dosing schedule. All 5 patients treated on the continuous weekly dosing regimen had a TRAE leading to study drug (talazoparib) discontinuation while none of the patients treated on the 1/1w schedule had either drug discontinued due to a TRAE. The continuous weekly dose regimen of this combination was deemed not tolerable. The safety profile for patients treated in Module 3b was comparable to that of the patients treated at the same dose level/schedule in Module 3a.

The dose level of 80 mg camonsertib Days 5-7 in combination with 0.25 mg QD talazoparib daily, 1/1w was expanded for evaluation as a potential RP2D. At this combination dose/schedule, grade ≥3 neutropenia was the most limiting TRAE (reported in 50% of patients and leading to dose reductions in 28.1% of patients). The overall rate of TRAEs leading to dose reductions at this dose/schedule was 43.8%.

The overall DLT rate for patients treated in Module 3a was 25%. All DLTs were hematologic. Based on isotonic regression of DLT rate versus dose levels, the highest dose administered (80 mg camonsertib Days 5-7 in combination with 0.25 mg QD talazoparib daily, 1/1w) had an estimated DLT rate below the target toxicity level (25%). Thus, this dose combination was also determined to be the MTD.

Efficacy:

The overall response rate for patients treated in Module 3a was 10.5% and the CBR was 44.7%. At the expanded dose level of 80 mg camonsertib (Days 5-7) in combination with 0.25 mg QD talazoparib (daily) 1/1w, the overall response rate was 11.1% and CBR was 44.4%. Patients who received the camonsertib and talazoparib combination in Module 3b following progression on camonsertib monotherapy did not exhibit clear clinical benefit. No patients (0/16) had a response and the CBR was 18.8%. The median PFS for patients treated in Module 3b was 7.1 weeks compared to 16.9 weeks for patients treated in Module 3a.

Pharmacokinetics: PK data will be presented upon completion of the study.

Conclusion:

This is an ongoing, exploratory, modular, Phase 1/2a, first-in-human, multi-center, open-label, non-randomized, dose-escalation, and dose-expansion study of camonsertib administered orally as a single agent or in combination with talazoparib or gemcitabine in patients with advanced solid tumors. There were 5 modules in this study; however, only information and data pertaining to Module 3 (camonsertib and talazoparib combination) are described herein. The Module 3 portion of this study was completed as of May 2024.

The dose level of 80 mg QD camonsertib Days 5-7 in combination with 0.25 mg QD talazoparib daily, 1/1w, was expanded to evaluate as a potential RP2D based on an acceptable DLT rate and preliminary evidence of anti-tumor activity. At this dose level, grade ≥3 neutropenia (reported in 50% of patients) was the most limiting TRAE, resulting in dose reductions in 28.1% of patients. Overall, 43.8% of patients at this dose level required a dose reduction due to a TRAE.

The rationale for evaluation of this combination was based on the expectation of synergistic efficacy. Due to the unacceptable safety profile of the combination on the continuous weekly dosing regimen, a less intensive intermittent weekly 1/1w regimen was evaluated. This dosing schedule was very well tolerated at the 50 mg QD camonsertib dose level; however, there was no clear evidence of anti-tumor activity. At the 80 mg QD camonsertib dose level, modest efficacy was observed (overall response rate of 10.5%);

however, tolerability was borderline acceptable, with >40% of patients requiring dose reductions due to AEs. Overall, the benefit-risk ratio of camonsertib in combination with talazoparib was deemed inadequate to warrant further pursuit of this combination in patients with advanced solid tumors.