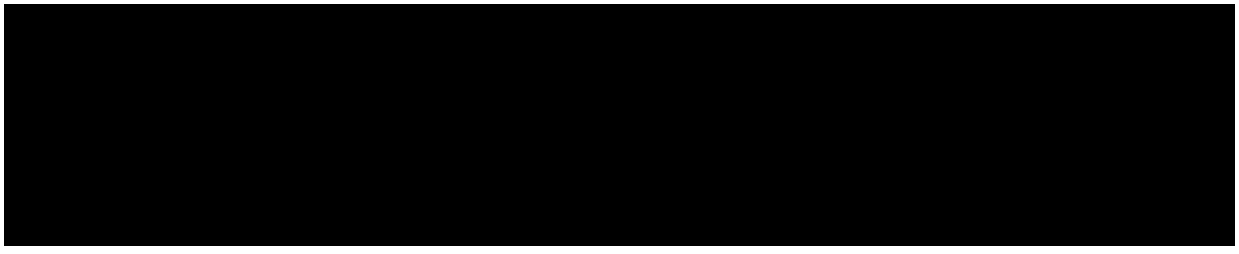
CLINICAL STUDY PROTOCOL

Title:	**Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination with Gemcitabine for the Treatment of Advanced Solid Tumors (MAGNETIC Study)**
Protocol Number:	RP-6306-02
Study Drug Names:	RP-6306, Gemcitabine
Development Phase:	1
Sponsor:	Repare Therapeutics 7210 Frederick-Banting Suite 100 St-Laurent, Quebec, H4S 2A1 Canada 101 Main Street Suite 1650 Cambridge, MA 02142 USA
Indication:	Advanced solid tumors
IND Number:	153,096
Date of Original Protocol:	12 July 2021
Date of Amendment 1	30 July 2021
Date of Amendment 2	26 October 2022
Date of Amendment 3	24 July 2023
Version of Protocol:	4.0
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation (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.

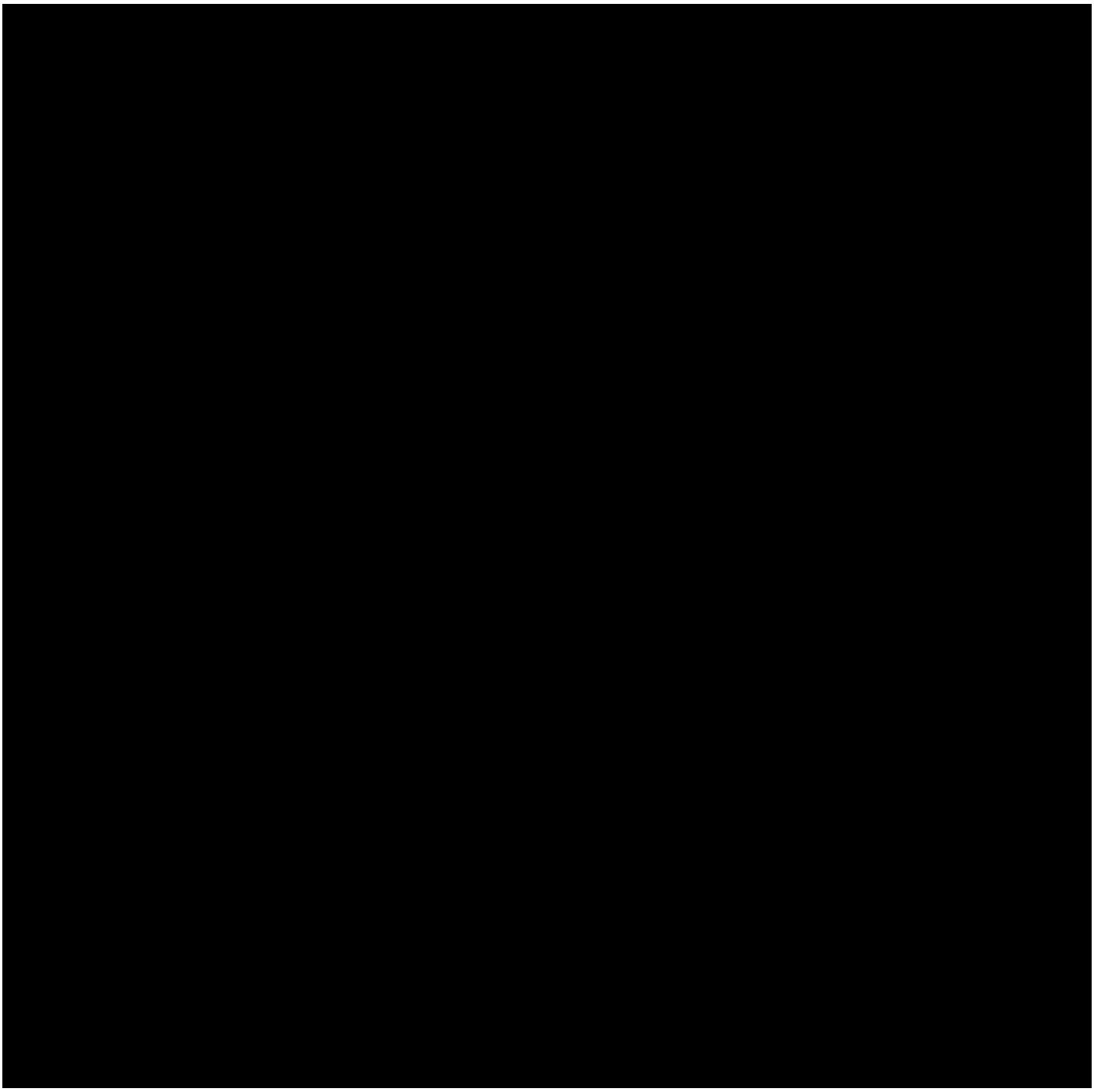


Name of Sponsor/Company: Repare Therapeutics	
Name of Investigational Products: RP-6306, Gemcitabine	
Name of Active Ingredients: RP-6306, Gemcitabine	
Title of Study: Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination with Gemcitabine for the Treatment of Advanced Solid Tumors (**MAGNETIC** Study: PK**M**YT1 Inhibitor **A**nd **G**emcitabi**NE** **T**reatment **I**n **C**ancer)	
Study Duration: Approximately 30 months	**Phase of Development:** 1
Number of Patients (planned): Approximately 150 evaluable patients are planned to be enrolled in this study.	

Objectives and Endpoints:

Primary Objectives	Primary Endpoints
To assess the safety and tolerability of RP-6306 in combination with gemcitabine in patients with eligible, advanced solid tumors	Incidence and severity of treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, electrocardiograms (ECGs), and use of concomitant medications
To define the maximum tolerated dose (MTD) and recommended Phase 2 Dose (RP2D) and schedule of RP-6306 in combination with gemcitabine	Dose-limiting toxicities (DLTs)

[redacted]



Study Design:

This is a multicenter, open-label, Phase 1 study to evaluate the safety and preliminary efficacy of RP-6306, a first-in-class, membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase (PKMYT1) inhibitor, given on a continuous or, if necessary, intermittent schedule in combination with gemcitabine for the treatment of patients with relapsed or refractory, advanced solid tumors (Figure A). Eligible patients must have a tumor harboring a CCNE1 amplification, a deleterious mutation in FBXW7 or PPP2R1A or other genetic alterations with mechanistic rationale agreed upon by the Sponsor and the Investigator. These genomic alterations are hypothesized to be synthetic lethal with RP-6306 and in preclinical mouse models were shown to be markedly sensitive to the combination of RP-6306 and gemcitabine.

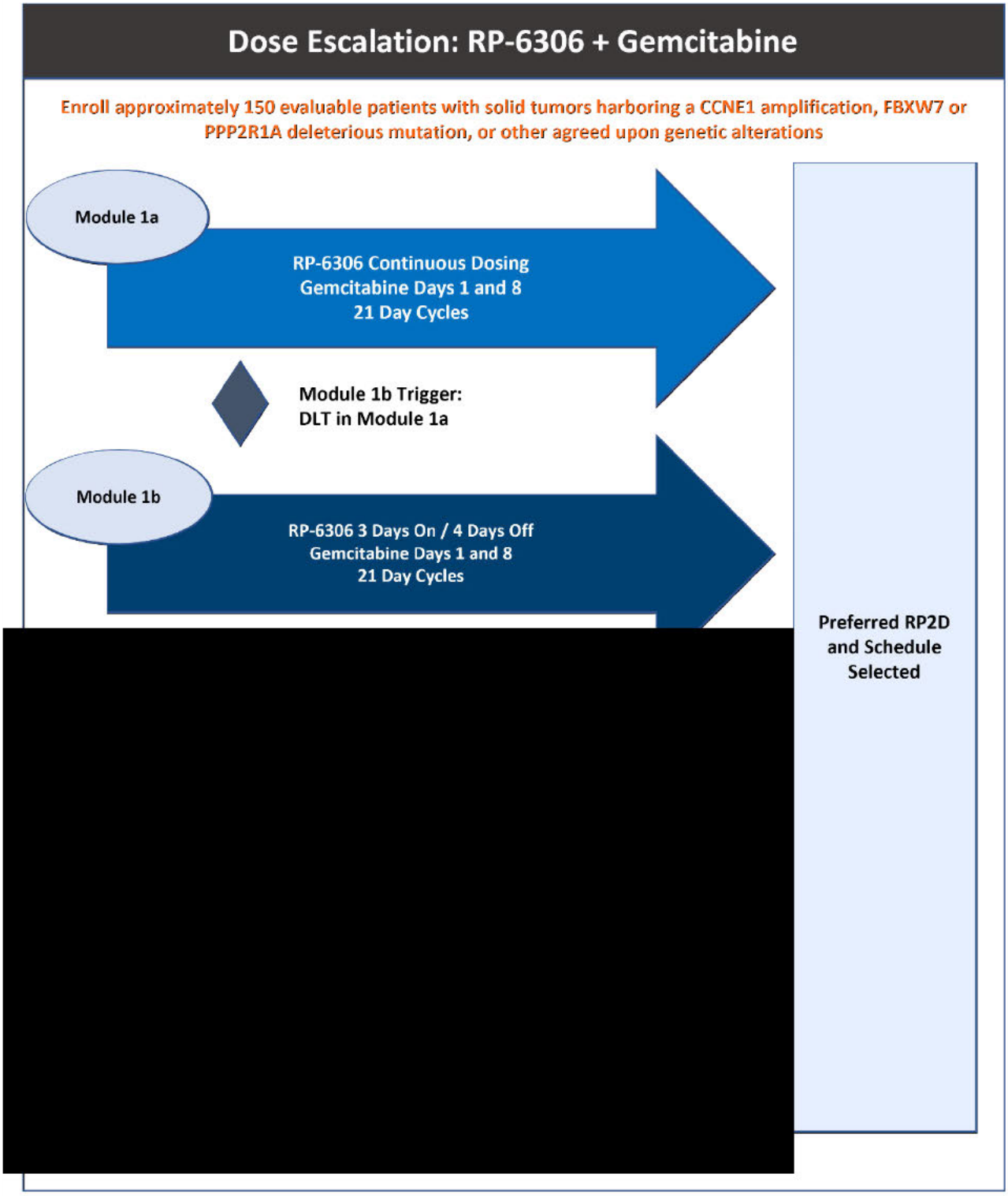
The study will follow a Bayesian optimal interval (BOIN) drug combination design to identify the MTD (dose level and dosing schedule for Module 1a, Module 1b, [redacted]) of RP-6306 and gemcitabine. Backfill cohorts with specific molecular alterations or cancer types will be enrolled to further evaluate the PK, pharmacodynamic and mechanism of action of biomarkers, safety and tolerability, and preliminary efficacy of the combination, as agreed upon by the Investigators and Safety Review Committee (SRC). The totality of safety, PK, pharmacodynamic, and preliminary efficacy data from each module will be used to establish a preferred RP2D and schedule.

All tumors will be profiled by local clinical tests validated in a College of Pathology (CAP)-, Clinical Laboratory Improvement Amendments (CLIA)-, or International Organization for Standardization (ISO)-certified laboratory to assure the eligibility of patients. Biomarker-positive tumors are defined as tumors that harbor either CCNE1 amplification, deleterious mutations (eg, hotspot, truncating, splice site, or frameshift) in FBXW7 or PPP2R1A, or other agreed upon genetic alterations. Patients will be enrolled based on local tumor or plasma NGS or FISH results for CCNE1 amplified tumors, and liquid biopsy or tumor NGS results for tumors that harbor FBXW7 or PPP2R1A deleterious mutations. Tumor NGS reports are required for enrollment of patients with cancers harboring other mutations agreed upon by the Sponsor and the Investigator. Sponsor-approved NGS tests include but are not limited to Guardant360, TSO-500, F1 liquid, Foundation Medicine F1CDx, Caris, Tempus, Paradigm, MSK IMPACT, Oncomine^{TM} V3, OncoPanel, or Qiagen Comprehensive. Additional NGS tests may be utilized for study enrollment upon Sponsor approval.

Molecular eligibility for the study will be centrally reviewed prior to the start of treatment to ensure NGS results are annotated consistently across all participating centers. Central review will re-annotate genomic results and ensure they meet the predefined, Sponsor-approved criteria for eligibility. CCNE1 amplification results deemed “equivocal” will not be allowed. Mutations in FBXW7 or PPP2R1A that are considered “likely pathogenic” may be allowed upon Sponsor review and approval.

Patients will continue treatment with RP-6306 and gemcitabine until disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, adverse event (AE), Investigator decision, withdrawal of consent, protocol non-compliance, pregnancy, or death. Patients requiring more than 2 continuous weeks off of planned study treatment for any reason will be discontinued from treatment unless the Investigator (in agreement with the Sponsor) believes and documents that the participating patient would derive clinical benefit with continued treatment.

Figure A: Study Design Schema



CCNE1=Cyclin E1; DLT=dose-limiting toxicity; FBXW7=F-box and WD repeat domain containing 7; PPP2R1A=protein phosphatase 2 scaffold subunit A; QD=once daily; RP2D=recommended Phase 2 Dose.
Note: Additional schedules may be tested based on safety, tolerability, and drug exposure data generated in Modules 1a, 1b, [redacted]

General Study Conduct:

Study evaluations and procedures will occur as outlined in the Schedules of Assessments (refer to Section 12.1). The study will consist of a Screening Period (Day -28 to Day -1, to determine eligibility), a Treatment Period (21- or 28-day cycles), an End-of-Treatment (EOT) Period (occurring within 7 days after the last dose of study treatment), a Safety Follow-up Visit (occurring 30 days ± 2 weeks after the last dose of study treatment, required for patients who discontinue treatment due to a Grade ≥2 drug-related AE that is ongoing at the time of discontinuation), and a Survival Follow-up Period (every 3 months ± 2 weeks for up to 6 months). The end of study is defined as the date of the last visit (including all follow-up visits) of the last patient in the study.

Safety:

Safety and tolerability will be reported by the Investigator, and evaluated by the Medical Monitor, Safety Officer, and SRC throughout the study. Assessments will include TEAEs, serious adverse events (SAEs), treatment discontinuations or dose modifications 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), ECGs, and others. All treatment-related AEs should be followed until resolution or documented Investigator decision stating that further improvement is not expected.

[redacted]

Laboratory Assessments:

Blood samples will be collected throughout the study to closely monitor safety parameters and characterize the PK profile of RP-6306 in combination with gemcitabine.

Patients being monitored for circulating tumor markers, such as cancer antigen 125 (CA-125), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), or any other tumor markers used for routine clinical evaluation, 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 treatment.

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

Tumor Tissue:

Sites must confirm availability of a recent archived tumor tissue, either tumor block (preferred) or 20 × 4 to 5 µm unstained slides, with verification of at least 30% tumor content and ship to the Sponsor's central laboratory during Screening or Cycle 1 Day 1 (+7 days). If less than 20 slides are available, the Sponsor must be contacted to gain approval. If archived tumor tissue is not available or is of insufficient quantity or quality, a fresh tumor biopsy should be obtained prior to initiating treatment. If, in the opinion of the Investigator, a fresh biopsy cannot be performed, the patient may still be eligible with Sponsor approval. Approval must be documented during Screening. Please refer to the Laboratory Manual for details on tumor sample requirements, collection, preparation, storage, and shipping procedures.

To fulfill secondary and exploratory endpoints, predose and on-treatment biopsies will be mandatory for patients with accessible lesions during dose escalation. Paired biopsies collected during dose escalation will be assayed to evaluate the degree of target engagement to aid in the selection of the RP2D and schedule. Biomarkers include, but are not limited to, a proximal target engagement biomarker phospho-cyclin-dependent-kinase 1 (CDK1) Thr14 and the distal proof-of-principle biomarker γ-H2AX.

Once the RP2D and schedule has been defined, 15 evaluable paired biopsies will be collected, and the Sponsor will notify the site when paired biopsies are no longer required. The paired biopsy must be deemed evaluable to support preplanned biomarker analyses, which means more than 15 participants at the RP2D and schedule may be required to have paired biopsies in order to collect 15 evaluable pairs. Target engagement will be correlated with efficacy and enrollment biomarkers CCNE1 amplification, or deleterious mutations (eg, hotspot, truncating, splice site, or frameshift) in FBXW7 and PPP2R1A or other agreed upon genetic alterations. To minimize risk, Investigators will preferably choose patients who have easily accessible tumors and in whom an outpatient procedure without general anesthesia is possible. If, in the opinion of the Investigator, biopsies cannot be performed, the patient may still be eligible to participate in the study with Sponsor approval. Approval must be documented during Screening.

Remaining tumor tissue and tumor derivatives such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) will be stored for future diagnostic development and to further understand response and resistance to RP-6306 and gemcitabine. Details are outlined in the Informed Consent Form (ICF).

Dose Finding:

This study aims to identify the RP2D and preferred dosing schedule of RP-6306 in combination with gemcitabine. RP-6306 will be given on a continuous schedule (Modules 1a [redacted] and intermittent schedule (Modules 1b [redacted]) as outlined below. Once triggered, Module 1b, [redacted] may proceed concurrently with Module 1a, and escalation and de-escalation will proceed independently as guided by the BOIN drug combination criteria. Patients will be enrolled into Modules 1a, 1b, [redacted] based on available slot openings at the time of signing the ICF and allocated to a cohort by the Medical Monitor with guidance from the SRC.

Module 1a:

The study will start at Dose Level 1A with 1 patient receiving 40 mg of once daily (QD), oral RP-6306 in combination with 800 mg/m^2 intravenous (IV) gemcitabine given over 30 minutes on Days 1 and 8 of each 21-day cycle. This dose of RP-6306 was chosen based on the observed tolerability of RP-6306 monotherapy in the MYTHIC study.

Dose escalation will proceed to the next higher dose level (Dose Level 2A) following BOIN criteria and dose escalation and de-escalation rules as follows:

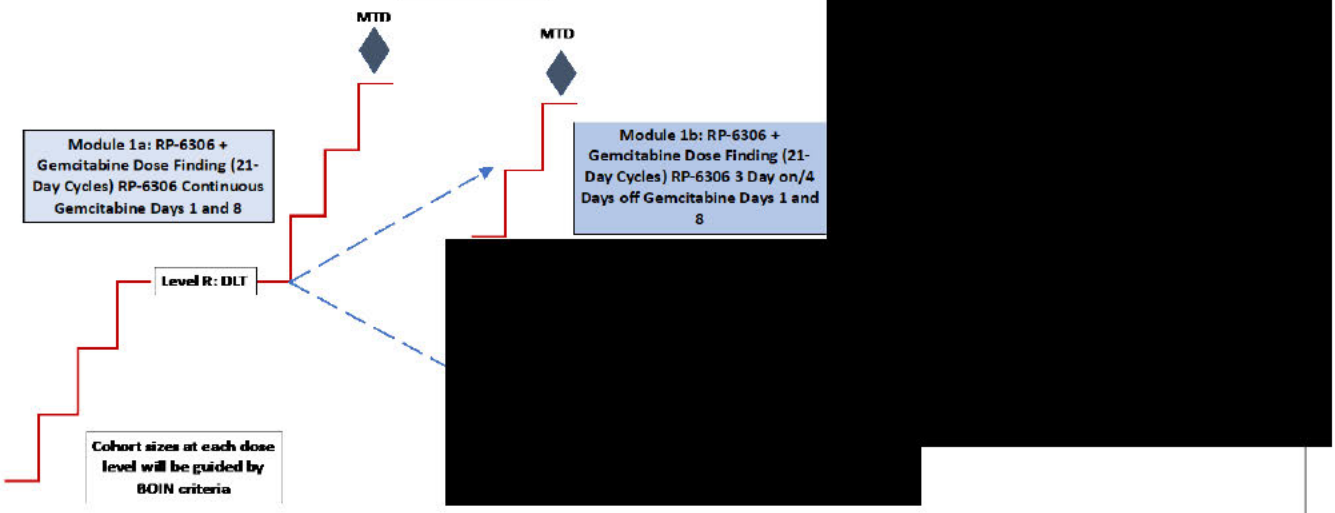
- Dose escalation will progress with increases of up to 100% RP-6306 until a DLT is observed (Level R in Figure B and Table A below). Dose decisions will depend on 2 or more evaluable patients completing the first 21-day treatment cycle.
- After Level R, RP-6306 will be de-escalated per BOIN drug combination criteria. For de-escalation at Level R, the next dose level of RP-6306 will be ≥25% lower than the current dose (rounded down based on capsule strength) or de-escalated down to the highest previously tolerated dose based on review of the toxicity patterns by the SRC. Gemcitabine can be de-escalated up to 25%. Only 1 drug in the combination will be de-escalated at any time. In addition to decreasing the daily dose level of RP-6306, de-escalation can involve a reduced frequency of dosing (eg, 5 days instead of planned 7 days or 2 days of RP-6306 rather than 3 days at the same dose level).
- After Level R, any dose escalation of RP-6306 or gemcitabine will follow the BOIN drug combination criteria as guided by the SRC. RP-6306 can continue with increases of 20% to 50% (R+1$^{\#}$), and dose escalation of gemcitabine can continue to a maximum of 1000 mg/m^2. Only 1 drug in the combination will be escalated at any time.

Module 1b:

Module 1b will be initiated after the first DLT is observed in Module 1a. In Module 1b, an intermittent dosing schedule of RP-6306 given 3 consecutive days on / 4 consecutive days off will be tested in combination with gemcitabine if confirmed safe by the SRC. When Module 1b is initiated, the starting dose of RP-6306 and gemcitabine will be the same as the highest total daily dose evaluated in Module 1a and will be given to a cohort of N≥2.

[redacted]

Figure B: Module 1a, 1b, [redacted] Escalation Schema



BOIN=Bayesian optimal interval; MTD=maximum tolerated dose.

Table A: Dose Finding Phase

Dose Level	Module 1a[a]: RP-6306 Continuous		Module 1b[a]: RP-6306 3 Consecutive Days On / 4 Consecutive Days Off	
	Total Daily RP-6306 Dose or % of Previous Dose	Gem Dose and Schedule	Total Daily RP-6306 Dose or % of Previous Dose	Gem Dose and Schedule
1D	40 mg	600 mg/m^2 Days 1 and 8	40 mg	600 mg/m^2 Days 1 and 8
1A[b] Starting Dose Level	40 mg	800 mg/m^2 Days 1 and 8	-	-
2A[b]	Up to 100% increase until Level R	800 mg/m^2 Days 1 and 8	-	-
R (DLT)	Expand cohort or de-escalate per BOIN drug	Same as current dose level	-	-

[redacted]

	combination criteria			
R+1[c]	20%-50% increase or 25%-100% decrease per BOIN drug combination criteria	Up to 1000 mg/m^2 Days 1 and 8	Same dose as continuous schedule for 3 days only	Up to 1000 mg/m^2 Days 1 and 8
R+N[c]	20%-50% increase or 25%-100% decrease per BOIN drug combination criteria	Up to 1000 mg/m^2 Days 1 and 8	Per BOIN drug combination criteria	Up to 1000 mg/m^2 Days 1 and 8

Gem=gemcitabine, BOIN=Bayesian optimal interval, DLT=dose-limiting toxicity, MTD=maximum tolerated dose.
R: Dose level at which pharmacologic activity observed
N: Any dose level after R+1
[a] Modules 1a, 1b, [redacted] may progress independently.
[b] Dose Levels 1A or 2A may be already Level R if early treatment-related toxicity is observed.
[c] The order of escalation (RP-6306 or gemcitabine) will be guided by BOIN drug combination criteria and agreed upon by the SRC.

If Dose Level 1A is not tolerated in Module 1a, Dose Level 1D will be explored. At Dose Level 1D, RP-6306 will be given at 40 mg daily on a continuous schedule and gemcitabine will be administered as an IV infusion at 600 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. If Dose Level 1D is tolerated and deemed safe by the SRC, gemcitabine dose will be maintained at 600 mg/m^2 given on Days 1 and 8 of each cycle and escalation of RP-6306 will proceed in increments of 25% to 50% in a continuous schedule. In addition, if Dose Level 1A is not tolerated using a continuous schedule, that same starting dose of RP-6306 (40 mg) and gemcitabine (800 mg/m^2) will be tested on a 3 consecutive days on / 4 consecutive days off dosing schedule. [redacted]

Based on the outcome of RP-6306 PK evaluation in the initial dose levels, a consideration for a twice daily (BID; same total daily dose as QD) RP-6306 administration will be discussed with the SRC. The decision to initiate BID dosing will be based on observed patient outcomes (eg, absence of toxicities, tumor response, or other pharmacologic activity) and PK parameters such as, but not limited to, $t_{½}$ is <12 hours or the C_{max}:C_{min} ratio is >10. The same dose escalation/de-escalation criteria will apply for BID dosing cohorts. If BID dosing is initiated, the SRC can elect to continue enrolling patients on a daily dosing arm or cease enrollment on this arm based on the data collected.

Maximum Tolerated Dose:

The BOIN drug combination design will be employed to find the MTD of continuous RP-6306 (Modules 1a [redacted] and intermittent RP-6306 (Modules 1b [redacted] in combination with

gemcitabine. [redacted] All Modules will be evaluated separately. The target toxicity rate is 25%. The approximate sample size will be 126 patients (114 evaluable + 10% non-evaluable) for dose finding in all Modules combined. DLTs occurring within the first treatment cycle will be used to assess the MTD. The expected number of maximum evaluable patients per module is 36 for Modules 1a and 1b [redacted]

The BOIN design uses the following rules, 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 1 of the 2 next higher dose levels (ie, 1 level increase of RP-6306 or 1 level increase of gemcitabine).
- If the observed DLT rate at the current dose is ≥0.298 (≥30%), de-escalate the dose to 1 of the 2 next lower dose levels (ie, 1 level decrease of RP-6306 or 1 level decrease of gemcitabine).
- Otherwise, stay at the current dose.

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

	Number of Evaluable Patients at Current Dose Level											
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
↑ if number of DLT ≤	0	0	0	0	0	1	1	1	1	1	2	2
Stay current dose if number of DLT =	NA	NA	NA	1	1	NA	2	2	2	2	3	3
↓ if number of DLT ≥	1	1	1	2	2	2	3	3	3	3	4	4
Elim if number of DLT ≥	NA	NA	3	3	3	4	4	4	5	5	6	6

BOIN = Bayesian optimal interval; ↑ = increase, ↓ = decrease, DLT = dose-limiting toxicity, Elim=eliminate, NA = not applicable, dose cannot be eliminated until at least 3 patients have been treated

Note: Number 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.

Dose finding starts at Dose Level 1A. The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at Dose Level 1A.

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 B). Please note the following:
    a. When the rule indicates dose escalation, initially only RP-6306 dose level is escalated. Escalation of gemcitabine level in addition to RP-6306 can occur after dose level R (Table A). After that, the decision to escalate gemcitabine or RP-6306 level will be based by which level is associated with a higher desirability score as provided in Table 35 (Appendix 3). When these 2 dose level combinations have the same desirability score (eg, no patients have been dosed at either of these 2 higher dose levels), choose one at the discretion of the SRC. When the rule indicates dose de-escalation, de-escalate the dose to one of the 2 next lower dose levels (ie., 1 level decrease of RP-6306 or 1 level decrease of gemcitabine), whichever has the higher desirability score as provided in Table 35 (Appendix 3). When they have the same desirability score, choose one at the discretion of the SRC.
    b. "Eliminate" means eliminate the current and higher doses (ie, all combinations of higher dose of RP-6306 and gemcitabine) from the study to prevent treating any future patients at these doses because they are overly toxic.
    c. When dose is eliminated, automatically de-escalate the dose to 1 of the 2 lower dose levels (ie, 1 level decrease of RP-6306 or 1 level decrease of gemcitabine). When the lowest dose is eliminated, stop the study for safety. In this case, no dose should be selected as the MTD.
    d. If none of the actions (ie, escalation, de-escalation, or elimination) is triggered, treat the new patients at the current dose.
    e. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the study for safety.
    f. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat Step 2 until the maximum sample size of 36 evaluable patients (Module 1a, 1b) [redacted] in the Dose Finding Phase is reached within each module, or transition if the number of evaluable patients treated at the current dose reaches ≥9 and the decision according to the Dose Escalation/De-Escalation Rules Table (Table B) is to stay at the current dose or a decision is made by the SRC to stop.

Dose decisions for escalation or de-escalation will depend on a minimum of 2 evaluable patients completing the first treatment cycle (Modules 1a and 1b: 21 days; [redacted]). Ultimately, dose (de)escalation decisions will be made by the SRC, in agreement with the Sponsor, based on totality of data in all patients evaluated in the study at the time of (de)escalation decisions.

After the study is completed, results from all DLT-evaluable patients including the relevant backfill cohorts will be included to assess the MTD. The dose for which the isotonic estimate of the toxicity rate is closest to and no higher than 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 RP-6306 and gemcitabine 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, PK, pharmacodynamics, and preliminary efficacy.

Dose-Limiting Toxicity Criteria:

Toxicity will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, unless otherwise specified. A toxicity will be considered dose-limiting if it occurs during the first cycle (Modules 1a and 1b: 21 days; [redacted]), meets the predefined 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.

A DLT is defined as any of the TEAEs listed below that is not clearly and incontrovertibly due to disease progression or extraneous causes.

DLTs will be defined as any of the following:

Treatment-Related Hematologic TEAEs:

- Grade 4 neutropenia lasting at least 7 days or Grade 4 neutropenia lasting < 7 days requiring the use of G-CSF
- Febrile neutropenia (defined as absolute neutrophil count [ANC] <1000 cells/μL 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 red blood cell (RBC) transfusion per local hospital guidelines

Treatment-Related Non-Hematologic TEAEs:

- Any Grade 3 treatment-related TEAE of >24-hour duration
- Any Grade 4 treatment-related TEAE of any duration

Any toxicity, regardless of the NCI CTCAE grade, resulting in discontinuation, Cycle 1 dose reduction, or treatment with less than 75% of planned doses will be reviewed by the SRC and will be considered a DLT if the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition, or concomitant medications. Any death not clearly due to disease progression or extraneous causes are DLTs.

TEAEs That Will **Not** Be Considered a DLT Include the Following:

- Grade ≥3 non-hematologic laboratory abnormalities that are not considered clinically relevant in the opinion of the Investigator or respond to medical intervention
- Grade 3 fatigue with duration <7 days and resolved to Grade ≤2, unless it recurs within the first cycle and is considered drug-related by the Investigator
- Grade ≥3 nausea/vomiting/diarrhea that has not been treated with optimal supportive care
- The use of red blood cell transfusion for anemia Grade <3 or the use of G-CSF for Grade <4 neutropenia based on institutional practice guidelines.

Determination of Dose-Limiting Toxicities:

The population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study and/or who have experienced a DLT at any time during the first treatment cycle. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of planned total doses of RP-6306 for the evaluated schedule, 100% of planned doses of gemcitabine, completes all required safety evaluations per Schedule of Assessments, and is observed at least until the end of the first treatment cycle.

If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the DLT-determining population described above, that patient will be replaced.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Written informed consent, according to local guidelines, signed and dated by the participating patient 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. Males or females ≥18 years old at the time of signature of the ICF.
3. ECOG performance status of 0 or 1.
4. All patients must have locally advanced or metastatic resistant or refractory solid tumors. Patients will be eligible only if standard or available curative therapy does not exist.
5. A recent archival tumor tissue sample must be shipped to the Sponsor's central laboratory. Patients who do not have archival tumor tissue that meets the specifications detailed in the Laboratory Manual should undergo a fresh tumor biopsy prior to treatment if it is considered safe to perform. If adequate archived tumor tissue is not available and/or a fresh biopsy cannot be performed, the patient may still be eligible with prior Sponsor approval.
6. All patient's tumors must have evidence of at least one of the following as reported by a local CLIA-certified or equivalent (ex-United States [US]) laboratory:
   a. CCNE1 amplification (non-equivocal) as determined by tumor or plasma NGS or FISH
   b. FBXW7 and/or PPP2R1A deleterious mutations (eg, hotspot, truncating, splice site, or frameshift) identified by either tumor or plasma NGS test
   c. Other genetic alterations with mechanistic rationale agreed upon by the Sponsor and the Investigator, identified by a tumor NGS test

   Note: *For all patients, an anonymized/redacted Molecular Pathology or other report(s) describing CCNE1, FBXW7, PPP2R1A or other genomic alterations should be submitted to the Sponsor or designee during Screening to confirm eligibility.*
7. Measurable disease as per RECIST v1.1.
8. Ability to comply with the protocol and study procedures detailed in the Schedule of Assessments.
9. Acceptable organ function at Screening, as evidenced by the following laboratory data:

a. Calculated creatinine clearance ≥60 mL/min using Cockcroft-Gault equation
b. Total bilirubin ≤1.5 × upper limit of normal (ULN) or <3.0 × ULN if known Gilbert's disease
c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × ULN or ≤5.0 × ULN in the case of presence of liver metastases

10. Acceptable hematologic function at Screening, defined as follows:
    a. No RBC or platelet transfusions or growth factors within 7 days of the first dose of treatment
    b. Hemoglobin ≥9.5 g/dL
    c. ANC ≥1500 cells/µL
    d. Platelet count ≥100 000 cells/µL
11. Negative pregnancy test (serum) for women of childbearing potential (WOCBP) at Screening.
    a. WOCBP is defined as fertile, following menarche and until becoming postmenopausal, unless permanently sterile. WOCBP who are sexually active and their partners must agree to use a highly effective form of contraception as detailed in Appendix 1 throughout their participation during the study and for 6 months after the last dose of study treatment.
    b. Women are considered postmenopausal and not of childbearing potential if they have had no menses for 12 months without an alternative medical cause or permanent sterilization methods including 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 1 FSH measurement is required.
12. 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 recommendations during their study participation and for 6 months after last dose of study treatment. Male patients must also refrain from donating sperm during their participation in the study and for 6 months after last dose of study treatment.
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).
14. Any prior radiation must have been completed at least 7 days prior to the start of study treatment, and patients must have recovered from any acute adverse effects prior to the start of study treatment.
15. Life expectancy ≥12 weeks after the start of the treatment according to the Investigator's judgment.

Exclusion Criteria:

1. Chemotherapy or small molecule antineoplastic agent given within 21 days or <5 half-lives, whichever is shorter, prior to first dose of study treatment. For drugs for which 5 half-lives is

≤21 days, a minimum of 10 days between termination of the prior treatment and administration of RP-6306 and gemcitabine treatment is required.

2. History or current condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
3. Patients who are pregnant or breastfeeding.
4. Known sensitivity to any of the ingredients of RP-6306 or gemcitabine.
5. Patients who are unable to swallow oral medications.
6. Prior treatment with a Wee1-like protein kinase (WEE1) inhibitor or PKMYT1 inhibitor.
7. Life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as ascites, coagulopathy, or encephalopathy), or other reasons which, in the Investigator's opinion, could compromise the participating patient's safety, or interfere with or compromise the integrity of the study outcomes.
8. Major surgery within 4 weeks prior to first dose of study treatment.
9. Uncontrolled, symptomatic brain metastases. Patients with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging within 4 weeks prior to the first dose of study treatment and any neurologic symptoms are controlled and stable), they have no evidence of new or enlarged brain metastases, and they are clinically stable and off steroids for at least 7 days prior to study treatment.
10. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg and diastolic BP ≥100 mmHg) despite adequate treatment prior to first dose of study treatment.
11. Active, uncontrolled bacterial, fungal, or viral infection, including hepatitis B virus, hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness. In equivocal cases, patients whose viral load is negative may be eligible. HIV seropositive patients who are healthy and low risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV positive patients should be evaluated and discussed with the 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.
12. Moderate or severe hepatic impairment (ie, Child-Pugh Class B or C).
13. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥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 (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

f. Clinically relevant electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia) or family history of sudden unexplained death or long ECG interval measured from the onset of the QRS complex to the end of the T wave (QT) syndrome

14. Mean resting QT interval corrected for heart rate (QTc) interval using the Fridericia formula (QTcF) >450 msec/male and >470 msec/female (as calculated per institutional standards) obtained from 3 ECGs taken ≥1 minute apart at study entry.
15. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
16. Patients who are receiving strong cytochrome P450 (CYP) 3A inhibitors or inducers within 14 days prior to first dose of study treatment (see Appendix 2).

Investigational Product, Dosage, and Mode of Administration:

RP-6306 will be supplied as immediate-release hard capsules for oral administration. RP-6306 will be orally self-administered with approximately 240 mL (~8 oz) of water. Patients taking RP-6306 at doses less than or equal to 120 mg (QD or BID) may take RP-6306 with a light meal, in avoidance of high fat food. For patients taking RP-6306 at doses >120 mg, a fast of 2 hours prior to and 1 hour after dosing is required. Patients will be initially instructed to take their dose at approximately the same time in the morning. RP-6306 will be taken once daily, on a continuous schedule in each cycle. If a BID dosing schedule is evaluated, the dose will be approximately an even split of the total daily dose and should be taken 12 (± 2) hours apart with food and drink withheld for at least 2 hours prior to and 1 hour post administration of the evening dose. In addition, an intermittent dosing schedule of 3 consecutive days on / 4 consecutive days off will be explored as guided by the SRC and should follow the administration recommendations as the continuous schedule.

Gemcitabine will be supplied as commercially available single-use vials for IV administration. Initially, gemcitabine will be administered IV at 800 mg/m^2 and, if safe, escalated to a maximum of 1000 mg/m^2 given over approximately 30 minutes. RP-6306 should be taken approximately 15 minutes to 1 hour prior to administration of gemcitabine.

During dose finding, intra-patient dose escalations are allowed at the discretion of the Investigator and with Sponsor approval. The dose of RP-6306 and/or gemcitabine may be escalated to a higher dose cohort only after that dose level has been declared safe and tolerable by the SRC. Dose interruptions and dose reductions to manage toxicities will be allowed for both study treatments and carefully monitored by the Investigator, Sponsor, and SRC.

Duration of Treatment and Follow-up:

Patients will continue treatment until disease progression by RECIST v1.1, AE, Investigator decision, withdrawal of consent, protocol non-compliance, 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 and agreed upon by the Sponsor), every 3 months (±2 weeks) until up to 6 months unless the patient withdraws consent to the study, the study is terminated, the patient dies or is lost to follow-up.

Safety:

All AEs in enrolled patients must be recorded regardless of the relationship of the AE to the study treatment from the date of first dose of study treatment through 30 days after the last dose of study treatment, or the start of new anticancer therapy if earlier than 30 days. SAEs considered related to study treatment are to be reported until the end of the Survival Follow-up Period which is up to 6 months after the last dose of investigational product (IP) or until lost to follow-up, patient withdrawal of consent, or whenever the investigator becomes aware thereafter.

During the Screening Period, all AEs related to study procedures are to be captured from the time ICF is signed to the first dose of study treatment. AEs considered not related to study procedures occurring during the Screening Period are to be captured as medical history.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored and recorded until the TEAE or SAE has resolved or stabilized, abnormal laboratory values have normalized, stabilized, or returned to baseline and there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up (LTFU), the Investigator determines that no further improvement is expected, or the patient has died. Any AE that occurs beyond the reporting period that the Investigator assesses as related to RP-6306 and/or gemcitabine should be reported to Repare Therapeutics.

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

Concomitant Medications:

Concomitant treatment and medication information will be collected from the time the patient signs the ICF until 30 days after their last dose of study treatment. The generic name of the drug (or trade name for combination drugs) must be specified along with the reason for use and duration of treatment. Additionally, all diagnostic, therapeutic, or surgical procedures, whether relating to malignancy or not, should be recorded in the electronic case report form (eCRF) including the date, indication, description of the procedure(s), and any clinical finding.

Any changes in documented, permitted concomitant treatments already being taken at the beginning of the clinical study must be recorded in the eCRF, noting the type of medication, the duration, and indication.

Prohibited Treatments:

Other investigational or anticancer agents are prohibited. Prophylactic antiemetics or prophylaxis for neutropenia, anemia, or thrombocytopenia will not be routinely provided from study start.

Statistical Methods:

Detailed methodology for summary and statistical analyses will be documented in the Statistical Analysis Plan (SAP).

Sample Size Calculation:

The approximate sample size for this study is 150. The sample size per module for the Dose Finding Phase is 36 evaluable patients in Modules 1a and 1b [redacted]. To allow 10% non-evaluable rate, the total sample size for the Dose Finding Phase would be 126. Approximately an additional 24 patients will be planned for backfill cohorts.

The population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT at any time during the first treatment cycle. Minimum safety requirements will be met if, during Cycle 1 of treatment the patient receives at least 75% of planned total doses of RP-6306 for the evaluated schedule, 100% of planned doses of gemcitabine, completes all required safety evaluations per Schedule of Assessments, and are observed at least until the end of the first treatment cycle. Depending on the toxicity profile of the combination and the number of dose levels required to establish the MTD/RP2D, the actual study sample size may vary.

Analysis Populations:

The following analysis populations will be used:

- DLT-Evaluable Population for dose decisions will be as defined above.
- The Safety Population, used for the assessment of overall safety and tolerability, will consist of all patients who receive at least one dose of study treatment. Patients will be assessed for safety based on the dose level in which they are enrolled.
- The Efficacy Population, used for the assessment of efficacy will consist of all patients who receive at least 1 dose of study treatment and had at least 1 post-baseline tumor assessment based on RECIST v1.1 or evaluable for tumor marker response (eg, Gynecological Cancer Intergroup [GCIG] for CA-125), or without post-baseline tumor assessment but discontinued the treatment due to clinical progression or death prior to any post-baseline tumor assessment. Patients should also have local confirmation of their genomic alterations.
- The PK Population, used for the assessment of PK endpoints, will consist of all patients who have sufficient RP-6306 plasma concentration data recorded to derive PK endpoints.

[redacted]

[redacted]

Safety Analysis:

Toxicity will be summarized by grade and type. All AEs will be listed, including the verbatim description, system organ class (SOC), and preferred term (PT).

Incidence of TEAEs, treatment-related TEAEs, TEAEs leading to death, SAEs, treatment-related SAEs, TEAEs leading to study treatment discontinuation or interruption, and TEAEs leading to dose modifications. Clinically relevant laboratory abnormalities (ie, laboratory abnormalities that result in treatment modification or require intervention) will be recorded as AEs. TEAEs will be further summarized by severity (according to NCI CTCAE version 5.0). Changes in clinical laboratory results (eg, hematology, chemistry, urinalysis, etc.), CTCAE graded laboratory toxicities, vital signs, ECOG performance status, PEs, and usage of concomitant medications and procedures will be summarized.

[redacted]

APPENDIX 1. CONTRACEPTIVE GUIDELINES

Women of childbearing potential who are sexually active must agree to the use of the following highly effective forms of contraception throughout their participation during the study treatment and for 6 months after the last dose of study treatment(s):

- 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

Partners of male patients can take combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Oral route
- Intravaginal route
- Transdermal route

Male patients with female partners of reproductive potential must use effective contraception during treatment and for 6 months following the final dose of study treatment (Clinical Trials Facilitation and Coordination Group 2014).

APPENDIX 2. STRONG CYP3A INHIBITORS AND INDUCERS

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

CYP3A=cytochrome P450 (CYP) 3A

Strong CYP3A Inducers

Inducers	Therapeutic class
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens

Inducers	Therapeutic class
Ivosidenib	Cancer Treatments
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal Medications
Lumacaftor	Cystic Fibrosis Treatments
Phenobarbital	Anticonvulsants

CYP3A=cytochrome P450 (CYP) 3A

Sensitive CYP3A Substrates

Inducers	Therapeutic class
Saquinavir	HIV antiviral
Indavir	HCV antiviral
Maraviroc	HIV antiviral
Lopinavir	HIV antiviral
Tipranavir	HIV antiviral
Darunavir	HIV antiviral
Efavirenz	HIV antiviral
Nelfinavir	HIV antiviral
Boceprevir	HCV antiviral
Daclatasvir	HCV antiviral
Velpatasvir	HCV antiviral
Telaprevir	HCV antiviral
Nevirapine	HIV antiviral
Sofosbuvir	HCV antiviral
Rilpivirine	HIV antiviral
Ritonavir	HCV antiviral
Estradiol	Oral contraceptive

CYP3A=cytochrome P450 (CYP) 3A; HCV=hepatitis C virus; HIV=human immunodeficiency virus

APPENDIX 3. DESIRABILITY SCORE TABLE FOR TRIAL CONDUCT

Table 35 is used to determine the dose for escalation or de-escalation when the BOIN rule in Table 5 indicates to do so. Suppose that the current dose level is (j, k), then the 2 higher dose levels eligible for escalation are (j+1, k) and (j, k+1), provided they exist and have not been eliminated from the study. To escalate, look up the desirability score of these 2 doses from Table 35 based on the DLT data observed at them, and choose the one with the higher desirability score for treating the next cohort of patients. The desirability score is based on DLT data already observed at that dose combination. If patients have not been dosed at that level, the desirability score is assigned a value of 8. If these 2 doses have the same desirability scores, choose one at the discretion of the SRC. Given specific DLT data, the desirability score is defined as the rank of that outcome, among all possible DLT outcomes, in terms of the posterior probability that the true DLT rate is located within the "stay" interval [0.197, 0.298], i.e, Pr(0.197 < pjk ≤ 0.298 |data). Thus, choosing a dose with the highest desirability score is equivalent to choosing a dose with the highest posterior probability that the true DLT rate is located within the "stay" interval [0.197, 0.298]. Note that "E" indicates that the dose is too toxic and should be eliminated from the study. If both higher doses should be eliminated, then the study should stay at the current dose level.

Likewise, to de-escalate, look up the desirability score of 2 lower dose levels, (j-1, k) and (j, k-1), provided they exist and have not been eliminated from the study. Then, choose the one with the higher desirability score for treating the next cohort of patients.

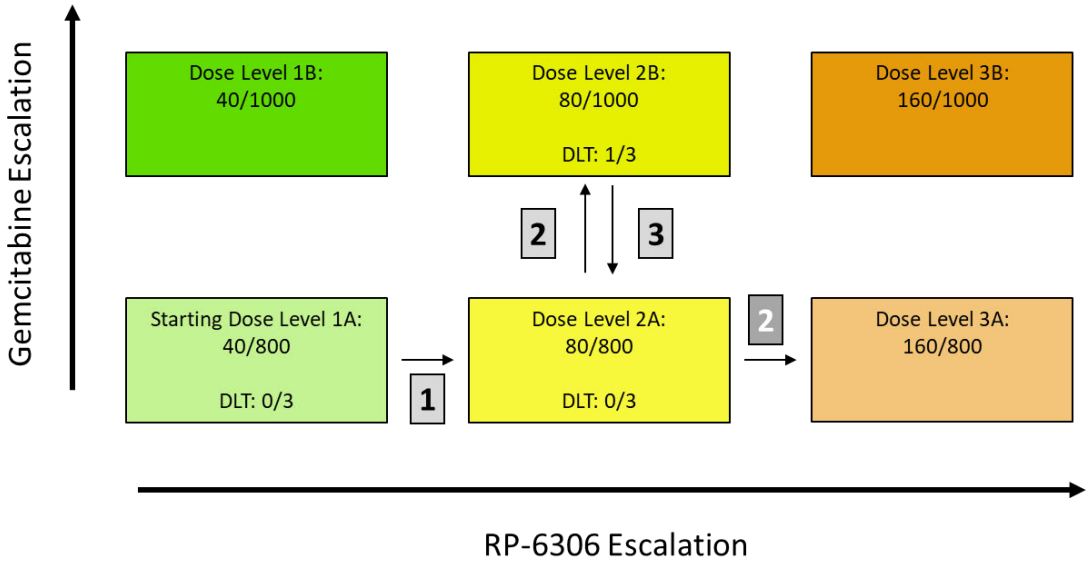
Table 35: Desirability Score Table (ϕ=0.25)

Num. eval.	Num. DLTs	Score
0	0	8
1	0	15
1	1	3
2	0	16
2	1	14
2	2	1
3	0	12
3	1	20
3	2	6
3	≥3	E
4	0	10
4	1	24
4	2	13
4	≥3	E
5	0	9
5	1	27
5	2	19
5	≥3	E
6	0	7
6	1	28
6	2	26
6	3	11
6	≥4	E
7	0	5
7	1	25
7	2	30
7	3	18
7	≥4	E
8	0	4
8	1	22
8	2	31
8	3	23
8	≥4	E
9	0	2
9	1	21
9	2	32
9	3	29
9	4	17
9	≥5	E

DLT=Dose-limiting toxicities; Eval.=evaluable; Num.=number.
"E" indicates that the dose is too toxic and should be eliminated from the study

A hypothetical scenario is provided to demonstrate how to use the desirability score to guide the dose escalation/de-escalation decision by SRC. The starting dose level is RP-6306 40 mg and gemcitabine 800 mg/m^2, hereafter referred as 40/800.

Figure 10: Hypothetical Scenario of Dose Escalation



1 Initially only escalate RP-6306 dose level

2 Escalation can be either 80/1000 or 160/800 with the same desirability score of 8 for these 2 dose levels. When there is a tie, dose escalation direction is made by SRC, in this case, assuming SCR decides to escalate to 80/1000

3 De-escalation to 80/800 which has a desirability score of 12, higher than 8 for 40/1000

40/800=RP-6306 40 mg + gemcitabine 800 mg/m^2; 80/800=RP-6306 80 mg + gemcitabine 800 mg/m^2; 160/800 = RP-6306 160 mg + gemcitabine 800 mg/m^2; 40/1000=RP-6306 40 mg + gemcitabine 1000 mg/m^2; 80/1000=RP-6306 80 mg + gemcitabine 1000 mg/m^2; 160/1000=RP-6306 160 mg + gemcitabine 1000 mg/m^2; DLT=dose-limiting toxicity; SRC=Safety Review Committee