# CLINICAL STUDY SYNOPSIS

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| **Title:** | **Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination With FOLFIRI for the Treatment of Advanced Solid Tumors (MINOTAUR Study)** |
| **Protocol Number:** | RP-6306-03 |
| **Study treatment Names:** | RP-6306, FOLFIRI |
| **Development Phase:** | 1 |
| **Sponsor:** | Repare Therapeutics<br>7210 Frederick-Banting<br>Suite 100<br>St-Laurent, Quebec, H4S 2A1<br>Canada<br>101 Main Street<br>Suite 1650<br>Cambridge, MA 02142<br>USA |
| [redacted] | [redacted] |
| **Indication:** | Advanced solid tumors |
| **IND Number:** | 153,096 |
| **Date of Protocol:** | 26 October 2022 |
| **Version of Protocol:** | 3.0 |
| **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. |
| **Confidentiality Statement:** | This document is confidential. It contains proprietary information of Repare Therapeutics (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study. |

# 1. SYNOPSIS

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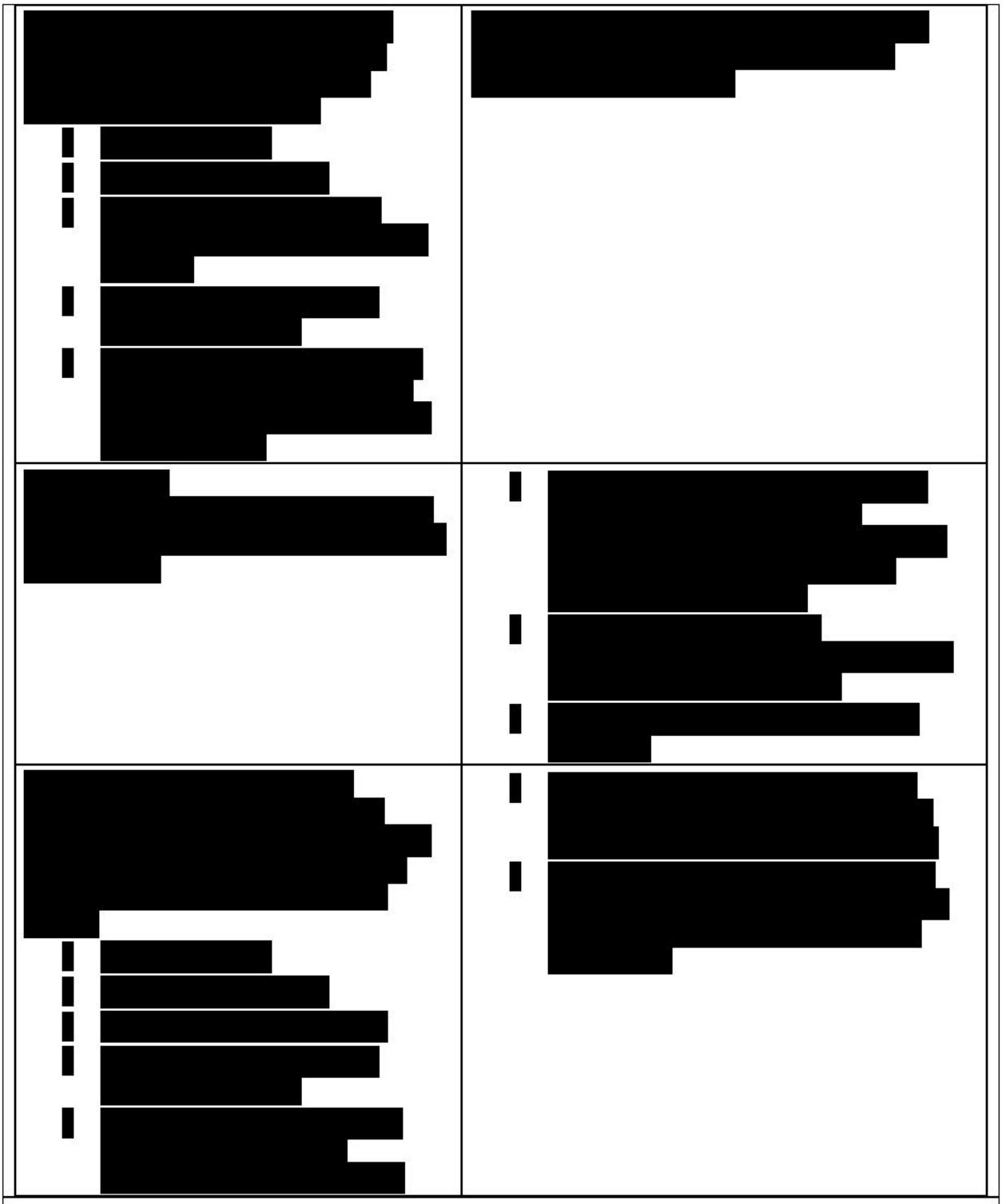
| **Name of Sponsor/Company:** Repare Therapeutics | |
| **Name of Investigational Products:** RP-6306, [Folinic Acid (Leucovorin), Fluorouracil, Irinotecan] (FOLFIRI) | |
| **Name of Active Ingredients:** RP-6306, [Folinic Acid (Leucovorin), Fluorouracil, Irinotecan] (FOLFIRI) | |
| **Title of Study:** Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination with FOLFIRI for the Treatment of Advanced Solid Tumors (**MINOTAUR** Study: PK**M**YT1 **IN**hibitor and F**O**LFIRI **T**re**A**tment of Solid T**U**mo**R**s) | |
| **Study Duration:** Approximately 30 months | **Phase of Development:** 1 |
| **Number of Patients (planned):** Up to 104 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 FOLFIRI 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 the recommended Phase 2 dose (RP2D) and schedule of RP-6306 in combination with FOLFIRI | Dose-limiting toxicities (DLTs) |
| **Secondary Objectives** | **Secondary Endpoints** |
| To assess the preliminary efficacy of RP-6306 in combination with FOLFIRI in patients with molecularly selected, advanced solid tumors | Best percent change in tumor size from baseline, objective response rate (ORR), best overall response rate, duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS) at 6 months, and overall survival (OS) at 12 months |
| To assess PK parameters of RP-6306 in combination with FOLFIRI | Plasma concentrations of RP-6306, irinotecan, and SN-38 with calculation of maximum observed plasma concentration within the dosing interval ($C_{max}$), time to maximum observed plasma concentration ($T_{max}$), area under the plasma concentration-time curve from time 0 to t ("t" being the longest time interval evaluable in all periods) ($AUC_{0\text{-last}}$), and other parameters as appropriate |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| [redacted] | [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 FOLFIRI for the treatment of patients with locally advanced or metastatic solid tumors (Figure A).

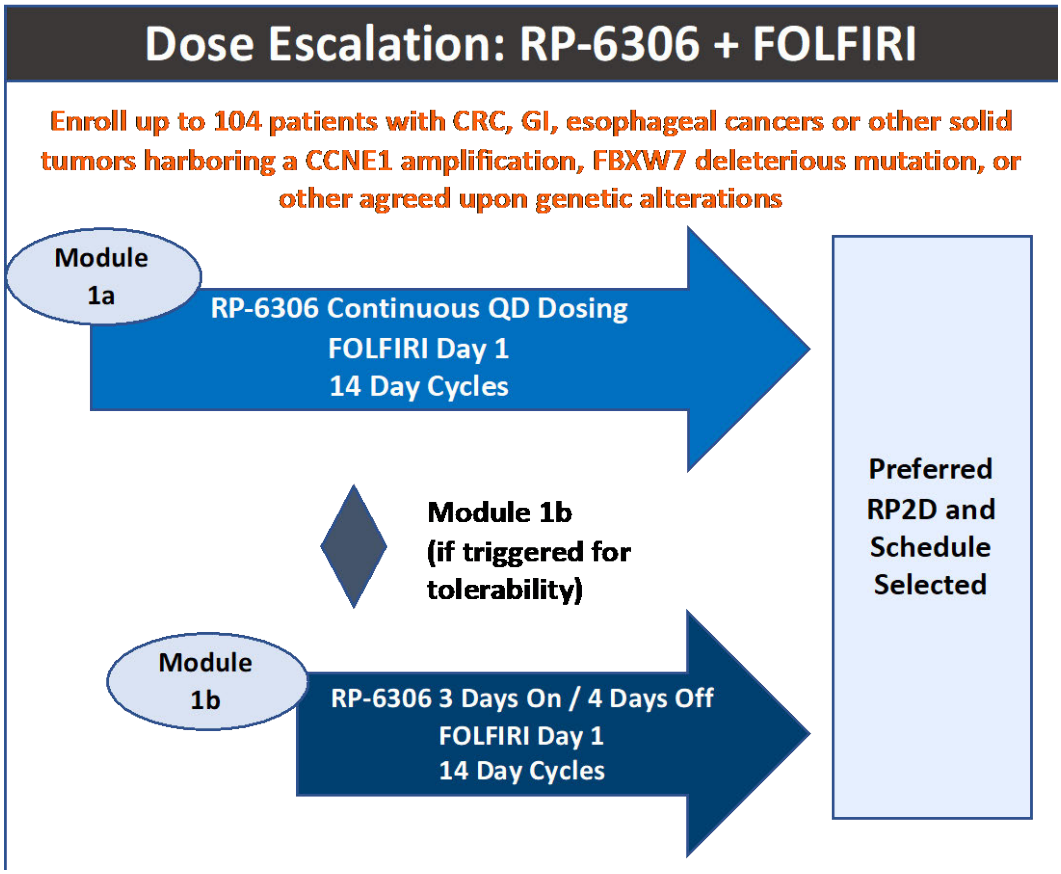
Eligible patients must have a CRC, GI, esophageal or other solid tumor harboring a CCNE1 amplification, deleterious mutation in FBXW7 or other genetic alterations with mechanistic rationale agreed upon by the Sponsor and the Investigator and, in the opinion of the Investigator, are candidates for FOLFIRI treatment. These genomic alterations are hypothesized to be synthetic lethal with RP-6306 and in nonclinical mouse models were shown to be markedly sensitive to single-agent RP-6306 and the combination of RP-6306 and irinotecan.

The study will follow a Bayesian optimal interval (BOIN) design to identify the MTD (dose level and dosing schedule for Module 1a and, if necessary, Module 1b) of RP-6306 and FOLFIRI. Backfill cohorts with specific molecular alterations or cancer types will be enrolled to further evaluate the PK, pharmacodynamic and mechanism of action 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 CCNE1 amplification, deleterious mutations (eg, hotspot, truncating, splice site, or frameshift) in FBXW7, 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 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™ V3, OncoPanel, or Qiagen Comprehensive. Additional NGS tests may be utilized for study enrollment upon Sponsor approval.

Patients will continue treatment with RP-6306 and FOLFIRI until disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, adverse event (AE), Investigator decision, withdrawal of consent, protocol noncompliance, 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 that the participating patient would derive clinical benefit with continued treatment.

**Figure A: Dose Finding Schema**




CCNE1=Cyclin E1; CRC=colorectal; FBXW7=F-box and WD repeat domain containing 7; GI=gastrointestinal; 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 and 1b.

**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 (14-day cycles), an End-of-Treatment (EOT) Period (occurring within 7 days after the last dose of study treatment), a Safety Follow-up Period (occurring 30 days ±2 weeks after the last dose of study treatment for all patients who are not cleared at the EOT visit, including patients with ongoing Grade ≥2 drug-related toxicities at the EOT visit), and a Survival Follow-up (every 3 months ±2 weeks for up to 12 months). The End of Study is defined as the date of the last visit (including all follow-up visits up to 12 months) of the last patient in the study. Patients will be followed for survival up to 12 months after EOT unless the patient withdraws consent to the study, the study is terminated, the patient dies or is lost to follow-up (LTFU).

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 AEs, 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, chemistry, and urinalysis), vital signs, 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.

Efficacy:

Patients must have a baseline tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of known sites of disease as clinically indicated. Positron emission tomography (PET)/CT may be used as clinically indicated. If the patient has had appropriate imaging scans (eg, routine clinical management) performed within 28 days prior to Cycle 1 Day 1, the results of those scans may be used as Screening tumor assessments, if they are of diagnostic quality and could be evaluated by a study center radiologist. Subsequent post-baseline tumor assessments will be performed following RECIST v1.1 guidelines, preferably in study center, but outside evaluation, if assessed by study radiologist, are acceptable. Response will be assessed by the study Investigator; however, all scans will be retained for a blinded independent central review, if deemed necessary.

For follow-up tumor assessments, CT/MRI scans of all sites of known disease will be performed every 6 weeks (±7 days) or sooner if clinically indicated, from start of treatment (Cycle 1 Day 1) for the first 3 assessments (~ first 5 months). Thereafter, tumor assessments will be performed every 9 weeks (±7 days). Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at least 4 weeks after the first indication of response, ideally at the next scheduled tumor assessment.

Tumor assessment should occur according to study schedule regardless of whether study treatment therapy is interrupted. If a patient discontinues treatment for a reason other than disease progression, withdrawal of study consent, or death, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

Efficacy will be reported as ORR, best overall response rate, CBR, DOR, and best percent change in tumor size from baseline per RECIST v1.1. Available data for PFS at 6 months and OS at 12 months will also be reported.

Laboratory Assessments:

Blood samples will be collected throughout the study to closely monitor safety parameters and characterize the PK profile of RP-6306, irinotecan, and irinotecan's active metabolite (SN-38) when co-administered.

Patients being monitored for circulating tumor markers, such as cancer antigen 125, prostate-specific antigen, carcinoembryonic antigen, 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 on Day 1 of each subsequent 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 safely performed, the patient may still be eligible with Sponsor approval. Approval must be documented during Screening. Please refer to Laboratory Manual for details on tumor sample requirements, collection, preparation, storage, and shipping procedures.

[redacted]

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 FOLFIRI. 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 FOLFIRI. The DLT evaluation period will consist of 2 cycles (28 days) of treatment. Initially, RP-6306 will be given on a continuous, once daily (QD) schedule (Module 1a) with dose escalation and de-escalation decisions guided by the BOIN drug combination criteria. If necessary, an intermittent dosing schedule (Module 1b) of 3 consecutive days on / 4 consecutive days off may be explored, and Module 1a may be terminated or proceed concurrently with Module 1b. Escalation/de-escalation will proceed independently as guided by the BOIN drug combination criteria. If both modules are run concurrently, patients will be enrolled into either Module 1a or 1b 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 1 with up to 2 patients receiving 40 mg QD, oral RP-6306 in combination with 180 mg/m$^2$ IV irinotecan given over 30 to 90 minutes, 400 mg/m$^2$ IV leucovorin given over 30 to 90 minutes with irinotecan, and 400 mg/m$^2$ IV fluorouracil bolus after leucovorin, then 2400 mg/m$^2$ IV continuous IV of fluorouracil over 46 hours (Days 1 and 2) of each 14-day cycle.

This dose of RP-6306 was chosen based on the observed tolerability and PK of RP-6306 monotherapy in the MYTHIC study. If Dose Level 1 is tolerated, the dose of RP-6306 will be escalated to 120 mg and the dose of irinotecan will be maintained at 180 mg/m$^2$ daily (Dose level 2). In addition, patients treated at Dose Level 1 will be eligible to receive RP-6306 at 120 mg QD, if Dose Level 2 has completed the DLT evaluation period and if agreed upon by the SRC. If Dose Level 1 is not tolerated, the dose of irinotecan will be de-escalated to 150 mg/m$^2$ and RP-6306 will be maintained at 40 mg daily (Dose level 1D).

After Dose Level 2, dose escalation of RP-6306 will proceed to the next higher dose level following BOIN criteria and dose escalation and de-escalation rules as follows:

- Dose escalation will progress with N≥2 patients 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 2 14-day treatment cycles.
- For de-escalation at Level R and thereafter, 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. In addition to decreasing the daily dose level of RP-6306, de-escalation can involve a reduced frequency of dosing (eg, 3 consecutive days on / 4 consecutive days off or 1 week on / 1 week off).
- Dose escalation of RP-6306 will follow the BOIN criteria as guided by the SRC. RP-6306 can continue with increases of 20% to 50% (R+1).

Intrapatient dose escalation may progress in subsequent patients once the next dose level is cleared by the SRC and the treating physician and the patient agrees that intrapatient dose escalation is desired.

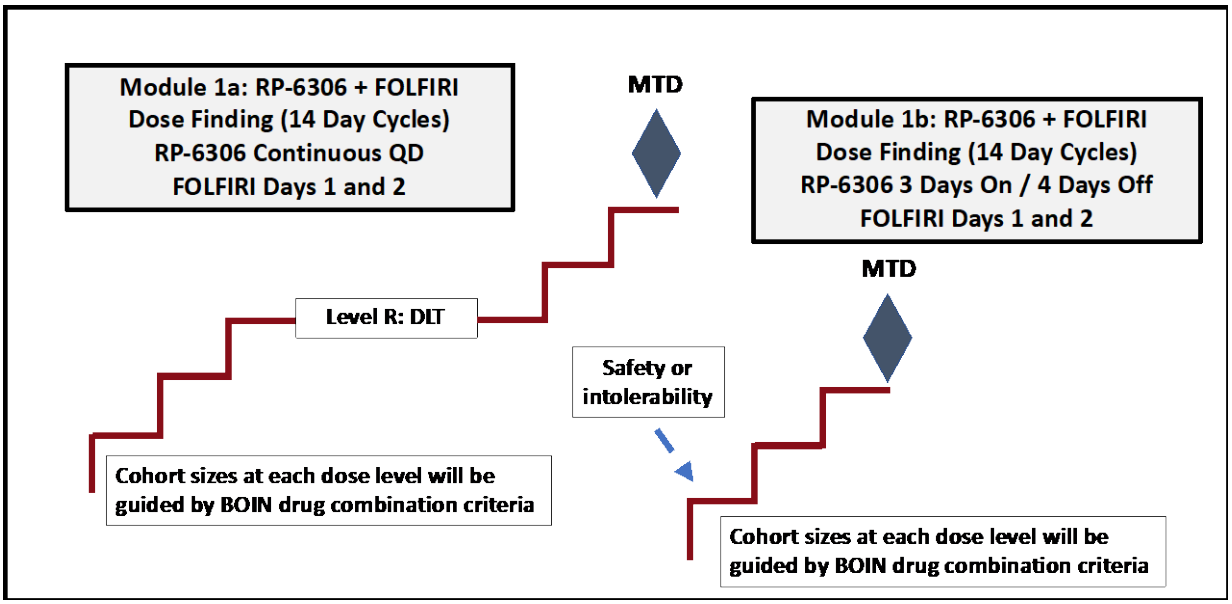
Module 1b:

If tolerability of continuous RP-6306 with FOLFIRI is limiting, Module 1b will be initiated if agreed upon by the SRC. 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 FOLFIRI. When Module 1b is initiated, the starting dose of RP-6306 and FOLFIRI will be the same as the highest total daily dose evaluated in Module 1a and will be given to a cohort of N≥2 patients. To allow better dose and schedule exploration early in the development, additional schedules may be evaluated that involve intermittent dosing (eg, 2 consecutive days on / 5 consecutive days off or 1 week on / 1 week off) depending on observed toxicities. The dose of RP-6306 or FOLFIRI will be increased or decreased per BOIN criteria independently of Module 1a until an MTD is established. Dose escalation decisions will be discussed with the SRC after at least 2 evaluable patients completing the first 2 14-day treatment cycles and based on the emerging safety and tolerability profile, and clinical PK/pharmacodynamic data across the entire patient population in Modules 1a and 1b.

In the event Modules 1a and 1b are explored concurrently, the Medical Monitor and SRC will prioritize slot allocation for each module. The highest dose level of RP-6306 in this study will not exceed the MTD of RP-6306 monotherapy identified in the MYTHIC study for a given schedule. The totality of safety, PK, pharmacodynamic, and preliminary efficacy data will be used to select a preferred RP2D and schedule for RP-6306 and FOLFIRI.

If anti-tumor activity is observed at a dose level that is lower than the current dose level being explored (after escalation has proceeded to a higher dose level), additional patients (N≤6), preferably with the same tumor/genomic alteration, may be enrolled at the lower dose level to further confirm safety and efficacy at that dose level. The relevant DLTs from the backfill cohorts will be included in the MTD and RP2D determination by the SRC. Additionally, intrapatient dose escalations for patients at a lower dose level will be allowed at the discretion of the Investigator, and with Sponsor approval and guidance by the SRC, if the higher dose level was deemed safe by the SRC.

**Figure B: Module 1a and 1b Escalation Schema**




BOIN=Bayesian optimal interval; DLT=dose-limiting toxicity; MTD=maximum tolerated dose; QD=once daily.

**Table A: Dose Escalation Tables**

**(A1) Dosing Regimens for Module 1a (Continuous RP-6306)[a]**

| Treatment Frequency | Drug | Route of Administration | Dose Level 1[b] (Starting Dose) | Dose Level 1[b] and above | Dose Level R | Dose Level R+1[c] | Dose Level R+N[c] |
|---|---|---|---|---|---|---|---|
| Once Daily | RP-6306 | Oral | 40 mg | 120 mg, then escalation up to 100% | Same as Current Dose Level | Per BOIN rules up to 20%-50% increase or MTD in MYTHIC | Per BOIN rules up to 20%-50% increase or MTD in MYTHIC |
| FOLFIRI once every 2 weeks on Day 1[d] | Irinotecan | IV over 30-90 min | 180 mg/m$^2$ | 180 mg/m$^2$ | Same as Current Dose Level | Up to 180 mg/m$^2$ | Up to 180 mg/m$^2$ |
| | Leucovorin | IV over 30-90 min concurrently with irinotecan | 400 mg/m$^2$ | 400 mg/m$^2$ | Same as Current Dose Level | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | Fluorouracil | IV bolus after leucovorin | 400 mg/m$^2$ | 400 mg/m$^2$ | Same as Current Dose Level | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | | **THEN** | | | | | |
| | Fluorouracil | IV continuous infusion; start on Day 1 over 46 hours only | 2400 mg/m$^2$ | 2400 mg/m$^2$ | Same as Current Dose Level | 2400 mg/m$^2$ | 2400 mg/m$^2$ |

*** If Dose Level 1 is not tolerated**

| Treatment Frequency | Route of Administration | Drug | Dose Level 1D[c] | Dose Level 2D[c] | Dose Level 3D[c] |
|---|---|---|---|---|---|
| Once Daily | Oral | RP-6306 | 40 mg | 40 mg | 40 mg |
| FOLFIRI once every 2 weeks on Day 1[d] | IV over 30-90 min | Irinotecan | 150 mg/m$^2$ | 120 mg/m$^2$ | 120 mg /m$^2$ |
| | IV over 30-90 min concurrently with irinotecan | Leucovorin | 400 mg/m$^2$ | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | IV bolus after leucovorin | Fluorouracil | 400 mg/m$^2$ | 400 mg/m$^2$ | No bolus |
| | **THEN** | | | | |
| | IV continuous infusion; start on Day 1 over 46 hours only | Fluorouracil | 2400 mg/m$^2$ | 2400 mg/m$^2$ | 2400 mg/m$^2$ |

BOIN=Bayesian optimal interval, DLT=dose-limiting toxicity, min=minute(s); MTD=maximum tolerated dose; MYTHIC=Phase 1 dose escalation study of RP-6306 monotherapy; N=any dose level after R+1; R=dose level at which DLT is observed; SRC= Safety Review Committee.

[a] Modules 1a and 1b will progress independently

[b] Level 1 or 2 may be Level R if early treatment-related toxicity is observed

[c] The order of escalation (RP-6306 or irinotecan in the FOLFIRI regimen) will be guided by BOIN drug combination criteria and agreed upon by the SRC.

[d] Investigators that would like to hold or modify the administration of the fluorouracil bolus and/or leucovorin require approval by the Repare Medical Monitor to do so.

**(A2) Dosing Regimens for Module 1b (Intermittent RP-6306, 3 Consecutive Days On / 4 Consecutive Days Off)[a]**

| Treatment Frequency | Drug | Route of Administration | Dose Level R+1[c] | Dose Level R+N[c] |
|---|---|---|---|---|
| Once Daily | RP-6306 | Oral | Per BOIN rules up to 100% increase or MTD in MYTHIC | Per BOIN rules up to 100% increase or MTD in MYTHIC |
| FOLFIRI once every 2 weeks on Day 1[d] | Irinotecan | IV over 30-90 min | Up to 180 mg/m$^2$ | Up to 180 mg/m$^2$ |
| | Leucovorin | IV over 30-90 min concurrently with irinotecan | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | Fluorouracil | IV bolus after leucovorin | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | **THEN** | | | |
| | Fluorouracil | IV continuous infusion; start on Day 1 over 46 hours only | 2400 mg/m$^2$ | 2400 mg/m$^2$ |

***If Dose Level 1 is not tolerated**

| Treatment Frequency | Route of Administration | Drug | Dose Level 1D[c] | Dose Level 2D[c] | Dose Level 3D[c] |
|---|---|---|---|---|---|
| Once Daily | Oral | RP-6306 | 40 mg | 40 mg | 40 mg |
| FOLFIRI once every 2 weeks on Day 1[d] | IV over 30-90 min | Irinotecan | 150 mg/m$^2$ | 120 mg/m$^2$ | 120 mg /m$^2$ |
| | IV over 30-90 min concurrently with irinotecan | Leucovorin | 400 mg/m$^2$ | 400 mg/m$^2$ | 400 mg/m$^2$ |
| | IV bolus after leucovorin | Fluorouracil | 400 mg/m$^2$ | 400 mg/m$^2$ | No bolus |
| | **THEN** | | | | |
| | IV continuous infusion; start on Day 1 over 46 hours only | Fluorouracil | 2400 mg/m$^2$ | 2400 mg/m$^2$ | 2400 mg/m$^2$ |

BOIN=Bayesian optimal interval; DLT=dose-limiting toxicity; IV=intravenous; min=minute(s); MTD=maximum tolerated dose; MYTHIC=Phase 1 dose escalation study of RP-6306 monotherapy; N=any dose level after R+1; R=dose level at which DLT is observed; SRC= Safety Review Committee.

[a] Modules 1a and 1b will progress independently.

[b] Level 1 or 2 may be Level R if early treatment-related toxicity is observed.

[c] The order of escalation (RP-6306 or irinotecan in the FOLFIRI regimen) will be guided by BOIN drug combination criteria and agreed upon by the SRC.

[d] Investigators that would like to hold or modify the administration of the fluorouracil bolus and/or leucovorin require approval by the Repare Medical Monitor to do so.

If Dose Level 1 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 irinotecan in the FOLFIRI regimen will be reduced to 150 mg/m$^2$ over 30 to 90 minutes on Day 1 of each 14-day cycle. If Dose Level 1D is tolerated and deemed safe by the SRC, irinotecan will be maintained at 150 mg/m$^2$, and escalation of RP-6306 will proceed in increments of 50% to 100% in a continuous schedule. If Dose Level 1D is not tolerated, Dose Level 2D will be explored. At Dose Level 2D, RP-6306 will be given at 40 mg daily on a continuous schedule and irinotecan in the FOLFIRI regimen will be reduced to 120 mg/m$^2$ over 30 to 90 minutes on Day 1 of each 14-day cycle. If Dose Level 2D is tolerated and deemed safe by the SRC, irinotecan will be maintained at 120 mg/m$^2$ and escalation of RP-6306 will proceed in increments of 50% to 100% in a continuous schedule. If dose level 2D is not tolerated, dose Level 3D will be explored, in which the bolus of fluorouracil will be eliminated from the regimen.

Based on the outcome of RP-6306 PK evaluation in the initial dose levels and emerging PK data in the MYTHIC (RP-6306-01) monotherapy study, 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, elimination half-life ($t_{½}$) is <12 hours or the $C_{max}$:$C_{min}$ ratio >10 (where $C_{min}$ is the minimum observed plasma concentration within the dosing interval). 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 design will be employed to find the MTD of continuous RP-6306 (Module 1a) and, if necessary, intermittent RP-6306 (Module 1b) in combination with FOLFIRI. The target toxicity rate is 25%. The maximum sample size will be 80 patients for dose finding in Modules 1a and 1b combined. DLTs occurring within the first 28-days (2 cycles) will be used to direct MTD finding.

The BOIN design uses the following criteria, 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 FOLFIRI).
- 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 FOLFIRI).
- Otherwise, stay at the current dose.

With the BOIN design, re-escalation after de-escalation is allowed and it is possible to escalate back to a dose level previously declared nontolerated. Prior to re-escalating to a previously nontolerated dose, an intermediate dose level may be explored. The final decision regarding degree of re-escalation will be determined by the SRC based on the totality of the safety and PK data.

For the purpose of overdose control, doses j and higher levels will be eliminated from further consideration if Pr(pj > 0.25 | data) > 0.95 and at least 3 evaluable patients have been treated at dose level j, where pj is the true DLT rate of dose level j, j = 1, …, 5. This posterior probability is evaluated based on the beta-binomial model yj | pj ~ binomial(pj) with pj ~ uniform(0, 1), where yj is the number of patients experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for

safety. When the lowest dose is eliminated, stop the trial for safety. The above dose escalation/de-escalation and elimination rule can be equivalently presented in Table B, which will be used to conduct the trial.

Table B provides information on the different dose decisions based on number of evaluable patients and the number of DLTs reported. Note, more than 6 patients may be exposed at a dose level to better define the MTD.

**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 1. The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at Dose Level 1. Dose decisions will depend on 2 or more evaluable patients completing the first 2 14-day treatment cycles.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table B. When using Table B, please note the following:
   a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
   b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
   c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.

d. 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 trial for safety.

e. 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 is reached or stop the trial early if the number of evaluable patients treated at the current dose ≥9 and the decision according to Table B is to stay at the current dose.

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 30% 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 FOLFIRI 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 2 cycles (28 days), 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 (a TEAE is any event that was not present prior to the initiation of study treatment or any event that worsens in either intensity or frequency following exposure to study treatment and for up to 30 days following the last dose of study treatment) listed below that is not clearly and incontrovertibly due to disease progression or extraneous causes.

DLTs will be defined as any of the following:

<u>Treatment-related Hematologic TEAEs:</u>

- Grade 4 neutropenia lasting at least 7 days or if granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor is given at any time
- Febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm$^3$ with a single temperature of 38.3ºC [101°F] or a sustained temperature of 38ºC [100.4°F] for >1 hour)
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with Grade ≥2 bleeding
- Grade 4 anemia or Grade 3 anemia requiring red blood cell (RBC) transfusion per local hospital guidelines

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

Treatment-related Nonhematologic TEAEs:

- Grade ≥3 nausea/vomiting/diarrhea that lasts >3 days despite optimal supportive care
- Any Grade 3 treatment-related TEAE of >24-hour duration
- Any Grade 4 treatment-related TEAE of any duration

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

- Grade ≥3 nonhematologic 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 2 cycles and is considered drug-related by the Investigator
- Grade ≥3 nausea/vomiting/diarrhea that has not been treated with optimal supportive care

**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 initial 28 days of the study. Minimum safety requirements will be met if, during the first 2 cycles of treatment, the patient receives at least 75% of planned total doses of RP-6306 and 100% of the planned dose of FOLFIRI, completes all required safety evaluations per Schedule of Assessments, and is observed at least until 28 days following the first dose of study treatment.

If a patient withdraws from treatment during the first 2 cycles 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 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 CRC, GI, or esophageal cancer(s) and radiographic evidence of progressing disease or any solid tumor with eligible molecular alterations (see criterion 6) that in the opinion of the Investigator are suitable for therapy with FOLFIRI regimen. Patients will be eligible if they have received no more than 3 prior treatment regimens, excluding adjuvant treatment. If the Investigator considers the patient a

candidate for FOLFIRI as initial treatment of newly diagnosed, metastatic, or advanced disease, the patient is eligible.

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 safely 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 (nonequivocal) as determined by tumor or plasma NGS or FISH
    b. FBXW7 deleterious mutations (eg, hotspot, truncating, splice site, frameshift) identified by either tumor or plasma NGS test
    c. Other genetic alterations with mechanistic rationale agreed upon by the Sponsor and the Investigator, determined by a tumor NGS test

    ***Note**: For all patients, an anonymized/redacted Molecular Pathology or other report(s) describing CCNE1, FBXW7 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. GFR ≥60 mL/min/1.73 $m^2$ using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or calculated creatinine clearance ≥60 mL/min using Cockcroft-Gault equation (or by 24-hour urine collection).
    b. Total bilirubin ≤1.5 × upper limit of normal (ULN)
    c. Aspartate aminotransferase and alanine aminotransferase ≤3.0 × ULN or ≤5.0 × ULN in the case of presence of liver metastases
10. Acceptable hematologic function at Screening:
    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/$mm^3$
    d. Platelet count ≥100,000 cells/$mm^3$
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 study treatment 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 include hysterectomy, bilateral salpingectomy, and bilateral

oophorectomy. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

12. Male patients with female partners of childbearing potential must follow a contraception method at least as conservative as Clinical Trial Facilitation Group recommendations during their 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 14 days prior to the start of study treatments, 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 FOLFIRI 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. Prior treatment with a PKMYT1 inhibitor or Wee1-like protein kinase (WEE1) inhibitor at any time, or irinotecan-based therapy given as an immediate prior therapy.
4. Patients who are pregnant or breastfeeding.
5. Known sensitivity to any of the ingredients of the study treatment.
6. Patient who are unable to swallow oral medications.
7. Life-threatening illness, medical condition, active uncontrolled infection, or organ system dysfunction (such as ascites, coagulopathy, or encephalopathy), or other reasons that, 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 for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms are controlled and stable), patients have no evidence of new or enlarged brain metastases, and patients are clinically stable and off steroids for at least 7 days prior to study treatment.
10. Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg; 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 (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness. In equivocal cases, patients whose viral load is negative may be eligible. HIV seropositive patients who are healthy and low risk for AIDS-related outcomes could be considered eligible. Eligibility criteria for HIV positive patients should be evaluated and discussed with the Sponsor's 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:
    e. Unstable angina pectoris
    f. Congestive heart failure
    g. Acute myocardial infarction
    h. Conduction abnormality not controlled with pacemaker or medication
    i. Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)
    j. 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 ≥1 minute apart at study entry.
15. Current treatment with medications that are well-known to prolong the QT interval (Appendix 2).
16. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
17. Patients who are receiving strong cytochrome P450 (CYP) 3A inhibitors or inducers within 14 days prior to first dose of study treatment (see prohibited concomitant medications in Appendix 3).

**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 after an overnight fast of at least 8 hours. Food and drink will be withheld for at least 1 hour after administration of RP-6306. Patients will be initially instructed to take their dose at approximately the same time in the morning. RP-6306 will be taken QD, on a continuous schedule in each 14-day cycle. If a BID dosing schedule is evaluated, the dose will be approximately an even split and should be taken 12 hours apart with food and drink withheld for at least 2 hours prior to and 1 hour post administration of the evening dose. If tolerability of RP-6306 is limited by continuous dosing, an intermittent dosing schedule of 3 consecutive days on / 4 consecutive days off may be explored as guided by the SRC and should follow the administration recommendations of the continuous schedule.

Irinotecan, leucovorin, and fluorouracil will be supplied as commercially available single-use vials. Initially, irinotecan will be administered IV at 180 mg/m$^2$ (100% of the approved dose level) given over 30 to 90 minutes on Day 1 of each 14-day cycle. Leucovorin will be administered concomitantly with irinotecan IV at 400 mg/m$^2$ (100% of approved leucovorin dose) given over 30 to 90 minutes on Day 1 of each 14-day cycle. Upon completion of the leucovorin infusion, a 400 mg/m$^2$ bolus of fluorouracil IV and then a 2400 mg/m$^2$ continuous infusion of fluorouracil (100% of approved fluorouracil dose) over 46 hours (Days 1 and 2 of each 14-day cycle) will be administered.

On Day 1 of each cycle, RP-6306 should be taken 15 minutes to 1 hour prior to the start of irinotecan and leucovorin.

During dose finding, intrapatient dose escalations are allowed at the discretion of the Investigator and with Sponsor approval. The dose of RP-6306 and/or irinotecan in the FOLFIRI regimen may be escalated to a higher dose level 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 and carefully monitored by the Investigator, Sponsor, and SRC.

**Duration of Treatment:**

Patients will continue treatment until disease progression by RECIST v1.1, AE, Investigator decision, withdrawal of consent, protocol noncompliance, pregnancy, or death. After treatment discontinuation, patients will be followed for survival. Survival Follow-up assessments will be done via telephone (or standard method used by participating centers as agreed upon by the Sponsor) every 3 months (±2 weeks) up to 12 months unless the patient withdraws consent to the study, the study is terminated, the patient dies or is LTFU.

**Safety:**

All AEs/SAEs in enrolled patients must be recorded regardless of the relationship of the AE/SAE 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 treatment 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 12 months after the last dose of investigational product (IP) or until LTFU, 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; abnormal laboratory values have normalized, stabilized, or returned to baseline and there is a satisfactory explanation for the changes observed; withdrawal of consent; or the patient is LTFU or has died. Any AE that occurs beyond the reporting period that the Investigator assesses as at least possibly related to RP-6306 and/or FOLFIRI should be reported to Repare Therapeutics.

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

**Concomitant Medications:**

Unless contraindicated, patients may receive atropine 0.25 to 1 mg IV/subcutaneous for cholinergic adverse effects (eg, early diarrhea). Diarrhea should be managed aggressively according to institutional guidelines and may include use of loperamide 4 mg at onset of diarrhea, then 2 mg every 2 hours until the patient is diarrhea-free for 12 hours. This may be combined with diphenoxylate/atropine if not adequately controlled with loperamide alone.

Patients with ileus, fever, or febrile neutropenia should receive antibiotics.

It is recommended that patients receive premedication with antiemetic agents according to institutional guidelines. A common antiemetic regimen includes 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT3 blocker (eg, oral ondansetron or granisetron). Physicians should also consider providing patients with an additional antiemetic regimen (eg, prochlorperazine) for subsequent use, as needed.

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 drugs are prohibited.

**Statistical Methods:**

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

Sample Size Calculation:

The maximum total sample size for this study is 104 patients. The maximum sample size for the Dose Finding Phase is 36 evaluable patients per Module (72 patients total if an intermittent dosing schedule is initiated). 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 initial 28 days (2 cycles) of the study. Minimum safety requirements will be met if, during the first 2 cycles of treatment, the patient receives at least 75% of planned total doses of RP-6306 for the evaluated schedule, 100% of planned doses of FOLFIRI, completes all required safety evaluations per Schedule of Assessments, and are observed at least until Day 28 since the first dose of study treatment. Thus, the possible total number per Module may be slightly higher at 40 patients (approximately +10%, 80 total patients). 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. Approximately an additional 24 patients will be planned for backfill cohorts.

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 were enrolled.
- The Efficacy Population, used for the assessment of efficacy, will consist of all patients who have measurable disease, are exposed to at least one dose of study treatment, and 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, irinotecan, or SN-38 plasma concentration data recorded to derive PK endpoints.

Efficacy Analysis:

Approximately 24 additional patients will be enrolled in backfill cohorts (N≤8 per cohort) to further evaluate the safety/tolerability profile in specific patient populations (eg, specific cancer types or patients that are high-risk for toxicities), [redacted]

The efficacy analysis will be summarized by dose combination and data from the backfill cohorts will be pooled with patients from the Dose Finding Phase that were treated at the RP2D (a minimum of 6 patients are expected to be treated at the RP2D during dose finding) when applicable.

Each cohort will be evaluated for ORR, best overall response rate, CBR, DOR, changes in tumor size, PFS at 6 months, and any available OS at 12 months.

[redacted]

Safety Analysis:

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

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 will be recorded. 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 parameters (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.

PK Analysis:

PK parameters for RP-6306, irinotecan, and SN-38 will be calculated using noncompartmental analysis or other modeling methods as well as using a population PK model: $AUC_{0\text{-last}}$, $C_{max}$, and $T_{max}$, and other parameters as appropriate.

[redacted]

# APPENDIX 1. CONTRACEPTIVE GUIDELINES

Women of childbearing potential, who are sexually active, must agree to the use of the following highly effective form 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. CONCOMITANT MEDICATIONS ASSOCIATED WITH A RISK OF QTC INTERVAL PROLONGATION AND/OR TORSADES DE POINTES

RP-6306 have not demonstrated adverse effects on QT prolongation in studies to date, however caution is advised when administering RP-6306 with any drug that may prolong QT.

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

Caution is advised when combining QT-prolonging medications or when using these medications in patients with electrolyte abnormalities. Below is a list of potential medications that may prolong QT interval. Patients receiving medications classified as “know risk” should be excluded. Please reach out to the Medical Monitor prior to enrolling any patient on RP-6306 or starting them on new medication while on study that you believe may prolong QT. Additionally, consulting with your local pharmacist is advised.

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

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

# APPENDIX 3. 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 3A.

## Strong CYP3A Inducers

| Inducers | Therapeutic Class |
|---|---|
| Rifampin | Antibiotics |
| Mitotane | Other antineoplastics |
| Avasimibe | Other antilipemics |
| Rifapentine | Antibiotics |

| Inducers | Therapeutic Class |
|---|---|
| Apalutamide | Antiandrogens |
| 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 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 3A; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

# APPENDIX 4. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS, VERSION 1.1

**Evaluation of Target Lesions**

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

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

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

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

**Evaluation of NonTLs**

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

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

**NonCR/NonPD:** Persistence of one or more nonTLs and/or maintenance of tumor marker level above the normal limits.

**PD:** Appearance of one or more new lesions and/or unequivocal progression of existing nonTLs. Unequivocal progression should not normally trump TL status. It must be representative of overall disease status change, not a single lesion increase.

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

**Evaluation of Best Objective Response**

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

### For Patients With Measurable Disease (ie, Target Disease)

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response | Best Overall Response When Confirmation Is Required[a] |
|---|---|---|---|---|
| CR | CR | No | CR | >4 wks confirmation[b] |
| CR | NonCR/nonPD | No | PR | >4 wks confirmation[b] |
| CR | Not evaluated | No | PR | |
| PR | NonCR/nonPD/ not evaluated | No | PR | |
| SD | NonCR/nonPD/ not evaluated | No | SD | Documented at least once 8 wks from first dose of study treatment[b] |
| PD | Any | Yes or No | PD | No prior SD, PR, or CR |
| Any | PD[c] | Yes or No | PD | |
| Any | Any | Yes | PD | |

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

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

[b] Only for nonrandomized studies with response as primary endpoint.

[c] In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.

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

### For Patients With Nonmeasurable Disease (ie, Nontarget Disease)

| Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| NonCR/nonPD | No | NonCR/nonPD[a] |
| Not all evaluated | No | Not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

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

[a] "NonCR/nonPD" is preferred over SD for nontarget disease since SD is increasingly used as an endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

# APPENDIX 5. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken 1982

# APPENDIX 6. SIMULATED OPERATING CHARACTERISTICS OF DOSE ESCALATION DESIGN

Table 22 shows the operating characteristics of the proposed design for this study with 5 scenarios involving various numbers and locations for the MTDs, based on 5000 simulations using the BOIN Design Desktop Program. The computer simulations allow operating characteristics of the design to be estimated, such as the expected proportion of patients who will be either under- or over-dosed, how accurately the true MTD will be identified and how many patients are expected to be exposed to each dose level. The proportion of patients over-dosed, defined as receiving a dose that had a true dose-limiting toxicity rate of >30%, ranged between 15.6% and 28.5% across all assumed dose-toxicity models. The operating characteristics also shows that the design selects one of the true MTD(s), if any, with high probability and allocates more patients to the dose levels with the dose-limiting toxicity rate closest to the target of 0.25.

**Table 1: Operating Characteristics of the Drug Combination BOIN design**

| | Dose Level | | | | | | Number of Patients | % Early Stopping |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | | |
| **Scenario 2** | | | | | | | | |
| **True DLT Rate** | 0.12 | 0.25 | 0.42 | 0.46 | 0.51 | 0.55 | | |
| **Selection %** | 24.8 | 62.4 | 11.1 | 1.5 | 0.1 | 0.0 | | 0.2 |
| **% Pts Treated** | 27.2 | 47.9 | 20.3 | 3.8 | 0.7 | 0.1 | 21.6 | |
| **Scenario 3** | | | | | | | | |
| **True DLT Rate** | 0.04 | 0.12 | 0.25 | 0.43 | 0.53 | 0.63 | | |
| **Selection %** | 1.2 | 30.9 | 57.2 | 10.0 | 0.6 | 0.0 | | 0.0 |
| **% Pts Treated** | 7.6 | 36.2 | 37.8 | 15.5 | 2.7 | 0.3 | 24.1 | |
| **Scenario 4** | | | | | | | | |
| **True DLT Rate** | 0.02 | 0.05 | 0.08 | 0.10 | 0.25 | 0.40 | | |
| **Selection %** | 0.1 | 3.7 | 8.3 | 22.0 | 52.0 | 13.9 | | 0.0 |
| **% Pts Treated** | 1.9 | 15.6 | 17.5 | 25.5 | 27.7 | 11.7 | 28.5 | |
| **Scenario 5** | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **True DLT Rate** | 0.02 | 0.04 | 0.06 | 0.09 | 0.11 | 0.25 | | | |
| **Selection %** | 0.1 | 2.0 | 4.4 | 9.5 | 24.2 | 59.9 | | | 0.0 |
| **% Pts Treated** | 1.5 | 14.4 | 16.5 | 18.0 | 25.1 | 24.5 | 27.9 | | |

BOIN=Bayesian optimal interval; DLT=dose-limiting toxicity; Pts=patients.

# Appendix 7. STUDY CONDUCT IN UNFORESEEN CIRCUMSTANCES

This appendix may be utilized by clinical trial sites during unforeseen circumstances that would result in increased risk associated with completion of the protocol conduct for study patients, such as during natural disasters (floods, tornadoes, earthquakes, hurricanes) or acts of people (e.g., acts of terrorism, riots, strikes, wars), and pandemics (e.g., COVID-19). These measures may be implemented if allowed by applicable country laws and regulations. These optional measures are put in place to preserve the risk-benefit for study participation. Measures should be documented by the site and reported by the Sponsor in the CSR.

This appendix describes possible adaptations to:

1. Consent Process
2. Investigational Medicinal Product Shipment
3. Patient Visits
4. Trial Assessments
5. Sample Collection
6. AE Reporting
7. Protocol Deviations

| Topic Requiring Adaptation | Section | Description |
|---|---|---|
| **Consent Process** | Inclusion Criteria<br>Exclusion Criteria | Original consent to enter the study must be performed in person at the clinical site. |
| | Written Informed Consent | If original consent to enter the study has been obtained, subsequent remote consent is allowable for patients unwilling or unable to come to study site. Alternative consents, in line with local/institutional guidelines, include such as usage of electronic signatures, faxing the signed consent forms, online consenting, oral consenting if the consent is obtained through audio/video communication through different applications, such as Skype. The specific consent process and the patient's consent should be documented in the patient's chart. The patient should re-sign the consent once able to visit the clinic. |

| | | |
|---|---|---|
| **Study Drug Shipment**<br><br>*All safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and study drug being dispensed to the patient for the first time* | Study Drug Shipping, Labeling and Storage | If potential border closures, flight restrictions and disruption affecting couriers, are observed during the enrollment of patients, this may cause delays in the shipment of the medication and customs clearance. The Sponsor will continue to monitor the impact of the unforeseen circumstances on the shipment of study medication as sites are evaluated for activation and/or additional IP shipments. If there are expected delays with medication importation or shipments, sites will be advised of the risk to screening and enrollment may be put on hold until the importation risks are mitigated, and medication supply can be provided to sites.<br><br>Alternative shipment methods, including providing study medication directly to study participants may be considered. |
| **Patient Visits**<br><br>*Screening and Day 1 of Cycle 1 must be conducted in person at the clinical trial site* | Schedule of Assessments and Pharmacokinetic Sampling | If the Investigator believes that travel to the study site for a study assessment would place the study patient at increased risk relative to the benefit of the in person assessment, the assessment can be conducted remotely through telemedicine (phone, Skype, etc.) by a trained clinician on the study team with the exception of the visits/assessments specified in the Schedule of Assessments. These can be billed as a visit while conducting standard assessments and to identify adverse events and ensure continuous medical care and oversight for this trial.). Visit changes will be considered a Protocol Deviation related to the unforeseen circumstances, such as COVID19, and should be documented by study standard procedures.<br><br>Changes in study visit schedules, missed visits, or patient discontinuations due to unforeseen circumstances may lead to missing information. Sites are being advised to capture specific information in the case report form that explains the basis of the missing data, including the relationship to the unforeseen circumstance for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19). |

| | | |
|---|---|---|
| **Study Assessments (including imaging and laboratory assessments)**<br><br>*All safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and study drug being dispensed to the patient for the first time* | Schedule of Assessments and Pharmacokinetic Sampling | Laboratory assessment can be completed locally and sent to the study site, taking into consideration study drug may get sent for more than 1 cycle worth, that safety labs must be reviewed by an Investigator to verify if the patient is fit for treatment continuation. Communication pathway should be agreed to with local office, including when to expect results, prior to completion of the assessment.<br><br>• Imaging assessment and protocol-mandated tumor samples or malignant fluid collection should be conducted as soon as they are considered safe and feasible; out of window assessments are preferable to a missed assessment. Visit changes will be considered a Protocol Deviation related to the unforeseen circumstances, such as COVID-19, and should be documented by study standard procedures. Performing an out of window imaging assessment is preferable to missing the assessment entirely. |
| [redacted] | | |
| **AE Reporting** | Collecting and Recording Adverse Events | If physical visits are reduced or postponed, the Investigators will continue collecting AEs from the patient through alternative means, e.g., by phone calls or telemedicine visits, as appropriate. |
| **Protocol Deviations** | Protocol Deviations | Protocol deviations (e.g., out of visit windows, etc.) should be captured per the usual study/institutional requirements. |

# Appendix 8. COUNTRY-SPECIFIC SUPPLEMENTS

**United Kingdom (UK)**

The following language apply to sites in the UK only.

Additional clarifications for contraceptive guidance for male participants who take RP-6306 or 5-FU (fluorouracil) are as follows:

1. Men must use a condom and partners who are WOCBP should be advised to use a highly effective contraception methods throughout the study and for 6 months after the last dose of study treatment.

2. Men should also be advised about cryopreservation of sperm prior to treatment because of the possibility of infertility due to therapy with study drug.