Statistical Analysis Plan

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Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination With FOLFIRI for the Treatment of Advanced Solid Tumors (MINOTAUR Study)

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ADaM	Analysis Data Model
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{0-8}	Area under the plasma concentration-time curve from time 0 to 8 hours post dose
AUC_{0-12}	Area under the plasma concentration-time curve from time 0 to 12 hours post dose
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 to infinite time
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to t ("t" being the longest time interval evaluable in all periods)
AUC_{ss}	Area under the plasma concentration-time curve at steady-state
BID	Twice daily
BOIN	Bayesian Optimal Interval
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CCNE1	Cyclin E1
CDISC	Clinical Data Interchange Standards Consortium
CDK	Cyclin-dependent kinase
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
CI	Confidence Interval
C_{max}	Maximum observed plasma Concentration
C_{min}	Minimum observed plasma concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
DBP	Diastolic Blood Pressure
DCO	Data Cut off

Abbreviation or special term	Explanation
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End-of-Treatment
FBXW7	F-box and WD repeat domain containing 7
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
LTFU	Lost to Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximal Tolerated Dose
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next-Generation Sequencing
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Exam
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PKMYT1	Membrane-associated tyrosine- and threonine-specific Cdc2-inhibitory kinase
PODS	Precision Oncology Decision Support
PPP2R1A	Protein phosphatase 2 scaffold subunit A
PR	Partial Response

Abbreviation or special term	**Explanation**
PSA	Prostate-Specific Antigen
PT	Preferred Term
QD	Once daily
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	Fridericia formula for corrected QT interval
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
$t_{½}$	Terminal Elimination Half-Life
TL	Target Lesions
T_{max}	Time to Maximum observed plasma concentration
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) prospectively describes the planned analyses for the study Protocol RP-6306-03 "Phase 1 Study of the PKMYT1 Inhibitor RP-6306 in Combination With FOLFIRI for the Treatment of Advanced Solid Tumors (MINOTAUR Study)" Version 3.0, which was issued on 26 October 2022. The SAP is in full conformity with the most current version of Good Clinical Practices (GCP), the FDA and ICH Guidelines for clinical trials. It contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy and safety. In addition, the datasets generated for this study will be compliant with the latest version of the CDISC standards for the SDTM and ADaM datasets.

This SAP mainly covers the primary and secondary objectives of the study. Analyses for some of the exploratory objectives will be addressed outside the SAP, where additional analysis plans may be developed to address these objectives. In addition, population pharmacokinetics (PK) and PK/pharmacodynamic modelling will be addressed outside of the SAP.

The purpose of this SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock. This SAP will be finalized and approved prior to the clinical database lock.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Module 1 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), and progression-free survival (PFS) at 6 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

[redacted]

2.2. Analysis Endpoints

The objective table provides information on the study objectives and analysis endpoints, split by primary, secondary and exploratory. The following section summarizes the primary, secondary, and exploratory analysis endpoints split by type of endpoints (safety, efficacy, PK, and biomarker).

2.2.1. Safety Endpoints

- DLTs
- Incidence of TEAEs, treatment related TEAEs, TEAEs leading to death, serious adverse events (SAEs), treatment related SAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose modifications (interruptions or reductions)
- Changes in clinical laboratory parameters (hematology, chemistry, urinalysis), CTCAE graded laboratory toxicities, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, ECG parameters including QTc, physical exams (PEs) and usage of concomitant medications

2.2.2. Efficacy Endpoints

Best percentage change in tumor size: defined as the largest decrease or smallest increase (in the absence of a decrease) in the sum of diameters of the target lesions (TLs) prior to progression or last evaluable assessment in the absence of progression.

- **Objective response rate** (**ORR**): defined as the proportion of patients with **confirmed** best overall response of complete response (CR) or partial response (PR) (i.e., 2 subsequent responses of either CR or PR at least 4 weeks apart) according to RECIST v1.1.
- **Best overall response rate**: defined as the proportion of patients with **confirmed or unconfirmed** response of CR or PR based on best overall response by investigators across all visits. Unconfirmed CR or PR will be defined as those patients with CR or PR only reported once in overall tumor assessment form by the Investigators according to RECIST 1.1.
- **Clinical benefit rate** (**CBR**): defined as the proportion of patients with a best overall response of CR or PR according to RECIST v1.1 based on Investigator's assessment, or duration on treatment of at least 16 weeks without evidence of progression.

Duration of response (**DOR, applicable only to patients with confirmed CR or PR**): defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of disease progression or death for any cause, whichever occurs earlier.

For patients who are alive without disease progression following response, DOR will be censored on the date of last evaluable tumor assessment.

- **Progression-free survival** (**PFS**): defined as the time from the first day of study treatment administration (Day 1) to disease progression as defined by RECIST v1.1 or death from any cause.
  - Patients who are alive and free from disease progression will be censored at the date of their last tumor assessment.
  - Any patient who dies in the absence of progression, and the death is >12 weeks after the last evaluable tumor assessment, will be censored for PFS at the date of their last evaluable tumor assessment. More details are provided in Section 8.1.9 and Table 8.

Detailed derivation of the endpoints can be found in Section 36.

[redacted]

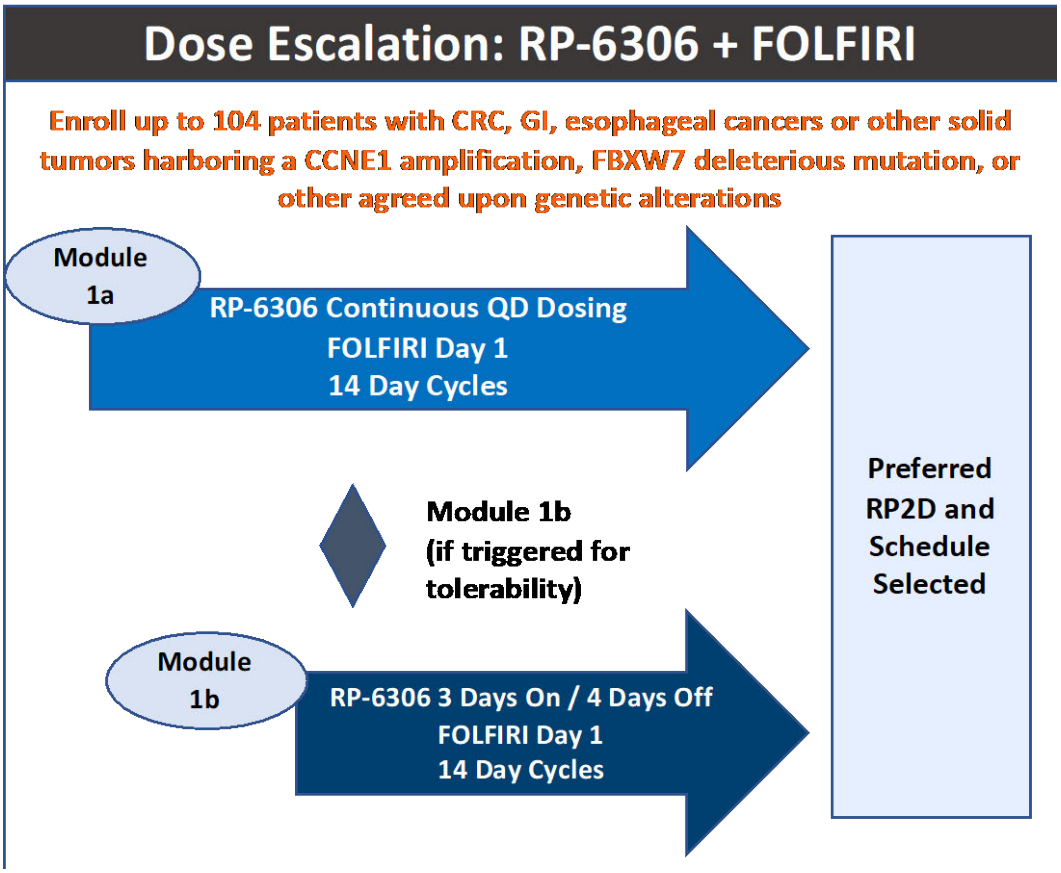
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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 1). Eligible patients must have a CRC, GI, esophageal tumor, or other solid tumors harboring CCNE1 amplification, deleterious mutation in FBXW7 and/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.

The study will follow a Bayesian Optimal Interval (BOIN) drug combination 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.

Figure 1: Module 1 Study Schema

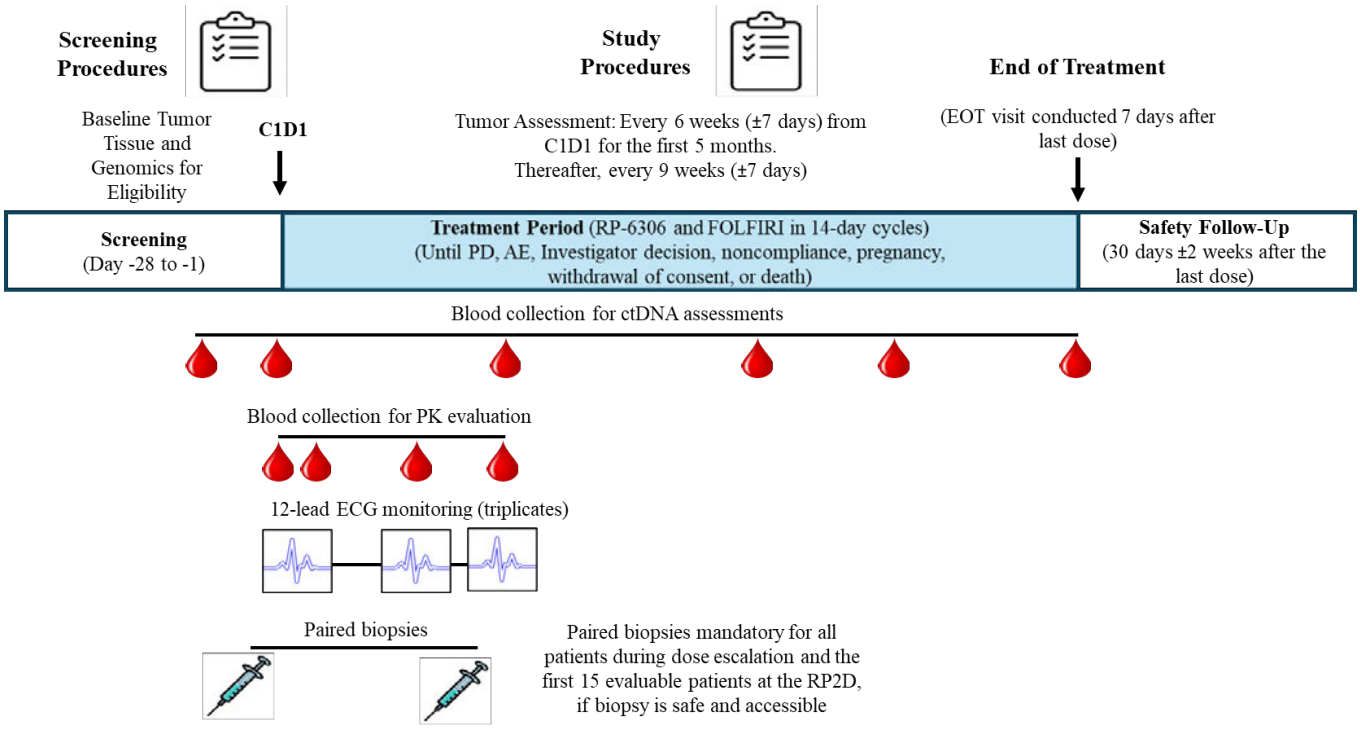


CCNE1=Cyclin E1; CRC=colorectal; FBXW7=F-box and WD repeat domain containing 7; GI=gastrointestinal; QD=once daily; RP2D=recommended Phase 2 dose.
Note: Additional schedules may be tested based on safety, tolerability, and drug exposure data generated in Modules 1a and 1b.

3.2. Schedule of Assessments

The study will consist of a Screening Period (Day -28 to Day -1) to determine eligibility, Treatment Period (14-day cycles), End-of-Treatment (EOT) Period (occurring within 7 days after the last dose of study treatment), and a Safety Follow-up Period (occurring 30 days ±2 weeks after the last dose of study treatment for all patients not cleared at the EOT visit, including patients with ongoing Grade ≥2 drug-related toxicities at the EOT visit (Figure 2). 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).

Figure 2: Study Conduct



AE=adverse event; C1D1=Cycle1 Day 1; ctDNA=circulating tumor deoxyribonucleic acid; ECG=electrocardiogram; EOT=End-of-Treatment; FU=Follow-up; PD=progressive disease; PK=pharmacokinetic; RP2D=recommended Phase 2 dose.

The start of the study is defined as the date when the first patient in the whole study signs an informed consent form (ICF).

The end of the study is defined as the date of the last visit (including all follow-up visits) of the last patient in the whole study.

See protocol for full details on the schedule of assessments.

The key procedures required in this study include:

- Tumor assessments (based on CT, PET, and/or MRI scan) according to RECIST v1.1 or as clinically indicated (see Appendix 4 of the protocol)
- PK samples throughout the study
- Baseline, on-treatment, and EOT blood samples
- Reporting all AEs occurring from the administration of the first dose of RP-6306 and FOLFIRI
- Paired biopsies
- ECG

A cycle of treatment is 2 weeks (14 calendar days).

3.2.1. Dose and Schedule Finding

This study aims to identify the RP2D and preferred dosing schedule of RP-6306 in combination with FOLFIRI. RP-6306 will be given on a continuous QD schedule (Module 1a) and intermittent schedule

(Module 1b) as outlined below. 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/m2 IV irinotecan given over 30 to 90 minutes, 400 mg/m2 IV leucovorin given over 30 to 90 minutes with irinotecan, and 400 mg/m2 IV fluorouracil bolus after leucovorin, then 2400 mg/m2 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/m2 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/m2 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 3 and Table 1 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).

Module 1b

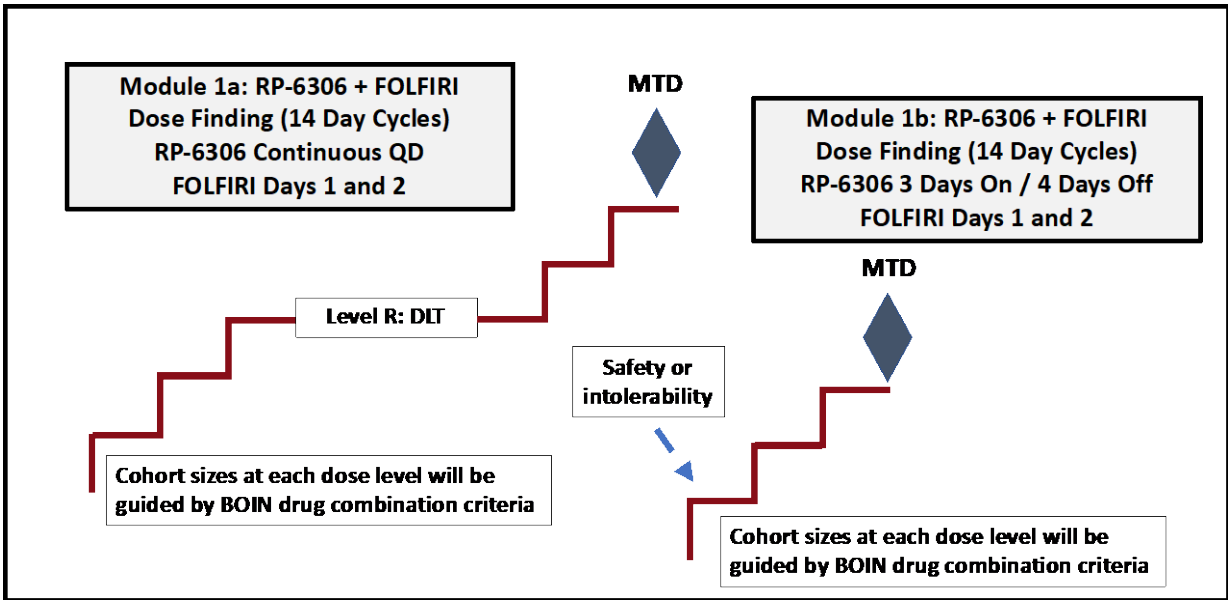
If tolerability of continuous RP-6306 with FOLFIRI is limiting, Module 1b will be initiated if agreed upon by the SRC. In Module 1b, an intermittent dosing schedule of RP-6306 given 3 consecutive days on / 4 consecutive days off will be tested in combination with FOLFIRI. When Module 1b is initiated, 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 3: Module 1a and 1b Escalation Schema



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

Table 1: Dose Escalation Tables

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/m2 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/m2, 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/m2 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/m2 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 (t½) is <12 hours or the Cmax:Cmin ratio >10 (where Cmin 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.

3.2.2. 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%. 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.

Table 2: Dose Escalation/De-Escalation Rules for the BOIN Design

Action	Number of Evaluable Patients at Current Dose Level											
	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 2. 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.

2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 2. When using Table 2, 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 for the corresponding module 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 the dose that at or lower than the MTD based on the totality of the safety, PK, pharmacodynamics, and preliminary efficacy.

3.3. Sample Size Considerations

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 (Section 11.1 of the protocol). 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 (Section 12.1 of the protocol), 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.

4. ANALYSIS POPULATIONS

4.1. DLT Evaluable Population

DLT Evaluable Population will consist of patients who have met the minimum safety evaluation requirements of the study and/or who experience a DLT at any time during the first two cycles (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 for the evaluated schedule, 100% of planned doses of FOLFIRI, completes all required safety evaluations per the Schedule of Assessments (refer to Section 12.1 of the protocol), and is observed at least until Day 28 since the first dose of study treatment.

4.2. Efficacy Population

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 without post-baseline tumor assessment but discontinued the treatment due to clinical progression or death prior to any post-baseline tumor assessment, and have local confirmation of their genomic alterations.

4.3. Safety Population

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.

4.4. Pharmacokinetic Population

The **Pharmacokinetic Population**, used for the assessment of PK endpoints, will consist of all patients who have sufficient RP-6306, irinotecan and/or SN-38 PK concentration data recorded to derive PK endpoints.

For all analysis populations, patients will be presented by the initial dose received.

5. DATA AND ANALYSIS CONSIDERATIONS

5.1. General Principles

All demography and safety data will be presented by the safety population, except for the DLT reporting which will be based on the DLT evaluable population. Assessment of anti-tumor activity will be based on the Efficacy Population and PK data will be presented by the PK Population.

Most of the analyses will be descriptive in nature. Unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, lower and upper quartile, minimum and maximum values) and the number and percentage of patients will be used for categorical variables. In general, missing data will be considered as missing and will not be imputed. Unless stated otherwise, percentages will be calculated out of the number of patients in the relevant analysis population.

Baseline will be the last assessment of the variable under consideration prior to first dose of RP-6306.

Unless stated otherwise, safety and efficacy data will be presented by assigned dose/schedule.

After determination of RP2D dose(s), safety and efficacy data may also be summarized by grouping dose levels based on RP2D and clinical relevance.

All DLT rates will be summarized by the assigned initial dose levels.

Summary statistics will be presented to the following degree of precision unless otherwise specified:

	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One more decimal digit than the raw data.
Standard deviation, Standard error	Up to 2 more than the raw data
Minimum, Maximum	The same decimal digit as the raw data.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

5.2. Study Day and Analysis Visit

Study Day will be calculated from the reference start date (defined as the date of first dose of study drug), and will be used to show start/stop day of assessments/events:

Study Day = (date of assessments/events - reference start date) if event/assessment is prior to the reference start;

Study Day = (date of assessments/events - reference start date + 1) if event/assessment is on or after the reference start.

There is no Study Day 0.

5.2.1. Analysis Visit

Baseline value will be the latest non-missing result obtained on or before the first dose of study treatment. The nominal visits will be used as analysis visits for the purpose of summarizing data over scheduled visit. If visits are clearly defined, no windowing algorithm will be used.

All recorded data will be included in the listings.

5.3. Handling of Missing Data

There will be no imputation of incomplete or missing data other than the dates mentioned below. No imputation will be performed for missing data elements for by-patient listings. However, the imputation will be implemented for summary tabulations, when applicable.

5.3.1. Missing/Partial Dates in Adverse Events

Missing Data Imputation for Adverse Event Start Dates

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

(1) Missing day only

- If the month and year are the same as the month and year of the first dose date, the first dose date will be used.
- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.
- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2) Missing day and month

- If the year is the same as the year of the first dose date, the first dose date will be used.
- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
- If the year is after the year of the first dose date, January 1st will be assigned to the missing fields.

(3) Missing day, month, and year (or only year)

- The first dose date will be used.

Missing Data Imputation for Missing Adverse Event Stop Date

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

(1) Missing day only

- The last day of the month will be assigned as the missing day.

(2) Missing day and month

- December 31 will be assigned to the missing fields.

(3) Missing day, month, and year (or only year)

- The event will be regarded as ongoing.

5.3.2. Missing/Partial Dates in Concomitant Medication

Missing Data Imputation for Concomitant Medication Start Dates

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

(1). Missing day only

- If the month and year are the same as the month and year of the first dose date, the first dose date will be used.
- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.
- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2). Missing day and month

- If the year is the same as the year of the first dose date, the first dose date will be used.
- If the year is prior to the year of the first dose date, December 31 will be assigned to the missing fields.
- If the year is after the year of the first dose date, January 1st will be assigned to the missing fields.

(3). Missing day, month, and year (or only year)

- Do not impute.

Missing Data Imputation for Missing Concomitant Medication Stop Date

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

(4) Missing day only

- The last day of the month will be assigned as the missing day.

(5) Missing day and month

- December 31 will be assigned to the missing fields.

(6) Missing day, month, and year

- Do not impute.

5.3.3. Missing/Partial Dates during Screening Visit or Prior to Study Treatment

The following rules apply to dates recorded during the screening visits (e.g., prior therapies/medications, initial diagnosis):

(1) Missing day only

- The first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.

(2) Missing day and month

- If the year is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.
- If the year is not the same as the year of the first dose of study drug, the date of the first of July will be used, unless other data indicates that the date is earlier.

(3) Missing day, month, and year

- No imputation will be applied.

If the imputed date is later than the first dose, then the date of the first dose will be used.

5.3.4. Missing/Partial Dates in Post-study Anticancer Therapy

Post-study therapy/radiotherapy start date:

If the stop date is non-missing and the imputed start date is after the stop date, the stop date will be used as the start date.

- If year is missing (or completely missing), do not impute.
- If year is present and month and day are missing:
  - If year is the same as the year of last dose date, impute as the last dose date + 1.
  - If year is greater than the year of last dose date, impute as January 1st.
- If year and day are present and month is missing:
  - If year is the same as the year of last dose date, and day is not greater than the day of last dose date, impute the month as the month of last dose date + 1.
  - If year or day is greater than the year or day of last dose date, impute the month as the month of last dose date.
- If year and month are present and day is missing:
  - If year and month are the same as the year and month of last dose date, impute as last dose date + 1.
  - If year or month is greater than the year or month of last dose date, impute day as first day of the month.

Post-study therapy/radiotherapy end date:

If the start date is non-missing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

- If year is missing (or completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present andmonth is missing, impute as December 31st.
- If year and month are present and day is missing, impute day as last day of the month.
- If the imputed end date is earlier than the observed/imputed post-study therapy/radiotherapy start date, the end date will be imputed as the same as the start date.

5.3.5. Missing/Partial Last Dose Date

Missing/incomplete last dose date from the treatment discontinuation page will be imputed as follows:

1. *Missing day only*

- If the treatment discontinuation reason is death, the death date will be used.

Else if the last available dosing date from dosing data matches the partial last dose date from the treatment discontinuation page, the last available dosing date will be used.

- Else the first day of the month will be used.

(2) Missing day and month

- If the treatment discontinuation reason is death, the death date will be used.
- Else if the last available dosing date from dosing data matches the partial last dose date from the treatment discontinuation page, the last available dosing date will be used.
- Else January 1st will be used.

(3) Missing day, month and year

- If the treatment discontinuation reason is death, the death date will be used.
- Else the last available dosing date will be used.

The imputed last dose date will be compared to the available study discontinuation date and the data cut off date. Then the earliest date will be used.

5.3.6. Relationship and Severity Imputation Rules for Adverse Events

Imputation will not be made for data listings and datasets. Missing severity and relationship will not be imputed. All AEs are expected to have non-missing severity (to toxicity grade) and relationship at the time of database lock.

6. DISPOSITION, DEVIATIONS AND PATIENT CHARACTERISTIC DATA

An overall patient disposition summary will be presented for all subjects to show the numberof unique patients who entered the study.

In addition, patient disposition will be presented by Module 1a or 1b and by dose/schedule with percentages based on the safety population. The following information will be presented for disposition:

- Included in each analysis population (DLT evaluation, safety, Efficacy and PK)
- Ongoing/discontinued study treatment at the data cut off
  - Including reasons for discontinuation of treatment as per the eCRF
- Ongoing/withdrawn/completion from study at the data cut off
  - Including reasons for study termination as per the eCRF

Disposition data will be listed for all patients and will include patient status, date of discontinuation from treatment, date of withdrawal from study and reason for treatment discontinuation and study withdrawal. In addition, the number and percentage of subjects by country and site will be summarized.

6.1. Protocol Deviations

There is no per protocol analysis population defined for this study, therefore patients will not be excluded from the data analysis and reporting based on deviations.

Any important deviations discovered during the trial either through the data collected on eCRFs or monitoring visits/reports will be listed and summarized. Deviation data may be exported into the database via third party data such as an excel file used by study monitors to track deviations (e.g., deviations collected via the clinical study management system, CTMS).

The following deviations will be considered important deviations:

- Patients who entered the study but did not fulfil the entry criteria.
- Treatment deviations such as wrong treatment received or incorrect dose during the study. Note, treatment delays or changes due to AE management are not considered treatment deviations. A review of relevant data may be required to confirm all important deviations in this category.
- Patients who received a prohibited concomitant treatment, including prohibited anti-cancer treatments.

If a patient has a delay in treatment or misses cycles due to the impact of COVID-19, their eligibility for inclusion in the analysis will be decided on a case-by-case basis prior to database lock.

Following review of all reported deviations and associated data and prior to database lock, other important deviation categories may be added. Only important deviations will be listed and summarized if appropriate. If the number of important deviations are few (<=5 patients), only listing will be provided.

6.2. Demographic and Baseline Characteristics

Demographics will be summarized by Module 1a or 1b and dose schedule for the safety population. Baseline demographic will include age at informed consent, age group (<65 and ≥65 years), gender, race, ethnicity, height (cm), weight (kg), BMI (kg/m^2). Baseline characteristics will include primary tumor type and ECOG status.

6.3. Genotype and Mutation Status at Enrollment

The genes and mutation status of patients based on local test at enrollment will be listed and summarized.

If a patient tests positive for more than one mutation/gene, the patient will be listed under the mixture of mutation/gene category for the baseline summary.

6.4. Disease Characteristics

The following disease characteristics will be summarized based on the Safety Population:

Disease History:

- Time since initial diagnosis (in years)
- Time since presentation of metastatic disease
- Primary tumor type
- Histology and grade of disease at diagnosis

Prior Anti-Cancer Therapy:

- Number of prior lines of treatment
- Prior irinotecan use
- Prior use of platinum containing regimen
- Information on last prior anticancer therapy:
  - Reason for administration (adjuvant, neoadjuvant, advanced/metastatic, etc.)
  - Best response
  - Disease progression (yes, no)
  - Time since end of last treatment in months
  - Duration of last treatment
  - Reason for end of regimen

6.5. Medical History

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized for the Safety Population, using System OrganClass (SOC) and preferred term (PT). The table will include the number and percentage of subjects and will be sorted in alphabetical order by SOC and PT. A subject will only be counted once within a class. A listing of

medical and surgical history will also be provided. In particular, cancer related medical history will be summarized by SOC and PT.

6.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients will be tabulated by WHO drug generic term for the Safety Population.

All prior and concomitant procedures (including transfusions) will be recorded from the Screening through to the EOT visit.

Prior medications will include medications which started prior to the date of first dose of study treatment. A summary table will present the numbers and percentages of patients who received prior therapy, including prior systemic anticancer therapy, prior radiation, prior surgery, and best response to the prior therapy, if known. Concomitant medications will include medications which started or were ongoing at the date of first dose of study treatment through to 30 days after the last dose of study treatment, or to the start of subsequent anticancer therapy, whichever occurs first. For Concomitant medications (including transfusions), 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.

The number of patients with a transfusion, reason for transfusion and type of transfusion will be provided in a listing.

Details of prohibited concomitant medications are provided in the protocol. To determine prohibited medications programmatically, a coded list of all prohibited medications will be provided by clinical team. Listings of prior and concomitant medications will display a flag for prohibited medications. This information will be used to identify protocol deviations.

7. SAFETY AND EXPOSURE DATA

Safety and tolerability will be assessed in terms of AEs, TEAEs, SAEs, DLTs, concomitant medications, PEs, vital sign measurements, clinical safety laboratory evaluations (hematology, serum chemistry, and urinalysis), ECOG performance scores, and ECGs including QTc.

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 28 days, it is deemed to be related to treatment and it meets the criteria defined in Appendix 1. The **DLT Evaluable Population** will be used as the analysis set during dose escalation to make dose decisions in determining the MTD. By-subject listings will be provided for DLTs (Cycle 2) using **DLT Evaluable Population**.

DLTs will be identified from the AE eCRF where the AE is selected as a DLT. All AEs reported as DLTs on the eCRF will be included even if they were not considered DLTs by the Safety Review Committee (SRC) during the study reviews.

The MTD for this study will be defined as the highest dose with the toxicity probability (DLT rate) <25%. The BOIN drug combination design will be employed to find the MTD of continuous RP-6306 (Module 1a) or intermittent RP-6306 (Module 1b) in combination with FOLFIRI. Module 1a and 1b will be evaluated separately based on target toxicity rate is 25%. Simulations confirm that with this study design, defining the MTD this way is equivalent tousing an isotonic regression with a descending pooled

adjacent violators algorithm, which isthe recommended method in the publication for BOIN study designs (Yuan et al., 2016).

7.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities(MedDRA) version 26.0 or more recent version (at the time of database lock) and graded according to NCI-CTCAE version 5. All laboratory test results will be classified for toxicity grade according to the NCI-CTCAE version 5 criteria.

DLTs will be listed and summarized based on the DLT Evaluable Population.

Treatment emergent adverse events (TEAEs) are those events that occur or worsen on or after the first dose of study drug up through 30 days post the last dose. Those events occurred after start of subsequent anticancer therapy will be excluded.

An overview summary table of the number and percentage of patients in each of the categories listed below will be presented. This summary will be presented based on all patients in the study (overall summary to summarize unique patients) and then repeated split by module 1a or 1b and dose/schedule (see Section 5.1 for general presentation format).

- All TEAEs
- Treatment related TEAEs (related to either study drug)
- DLTs
- TEAEs with ≥ CTCAE Grade 3
- Treatment-related TEAEs with ≥ CTCAE Grade 3 (related to either study drug)
- Serious TEAEs
- Treatment-related serious TEAEs (related to either study drug)
- TEAEs with outcome of death
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose modification (i.e., dose reduced or dose interrupted) of study treatment

TEAEs will be summarized by system organ class (SOC), preferred term (PT), and by NCI CTCAE toxicity grade (where applicable). For summary tables, an AE that occurs more than once within a SOC and/or PT for the same patient will be counted only once using the worst NCI toxicity grade experienced.

Number and percentage of participants with TEAEs will also be presented by PT only. This summary will be sorted in decreasing order of frequency based on overall safety population.

For the summary tables related to toxicity grades, if there are two or more TEAEs (or AEs) with same SOC or PT and different toxicity CTCAE grades for the same subject, only the maximum toxicity grade of AE be counted.

Data listing will be provided for all TEAEs, TEAEs with ≥ CTCAE Grade 3 and serious TEAEs.

An AE table of most frequently occurring TEAEs, showing all events in at least 5% of patients, will be summarized by preferred term, by decreasing frequency based on all patients. This cut-off may be modified after review of the data.

TEAEs with outcome of death, leading to discontinuation of study treatment or leading to dose reduction, dose interruption or discontinuation of study treatment will be summarized by preferred term. Corresponding listings will be provided. If the number of occurrences is low (e.g., when ≤ 5 patients involved), only listing will be provided. If necessary, tabulated by preferred term depending on the number of TEAEs reported for those categories.

For patients who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group for summarizing. Any AE occurring before the first dose of study treatment will be included in the data listings but will not be included in the summary tables of AEs.

Summary tables will include only treatment-emergent adverse events (TEAEs). Non-TEAEs will be listed but will not be included in the summaries. Note that those events with onset after start of subsequent anticancer therapy will be excluded from the TEAE summary.

Pooled rash will include preferred terms of Rash Maculo-popular, Pruritis, Rash, Skin Exfoliation, Erythema, Dermatitis Contact, Eczema, Flushing, Rash Erythematous, and Rash Pruritic.

A listing of all deaths and causes of deaths will be provided.

7.2. Treatment Exposure

Exposure will be derived for RP-6306 and FOLFIRI respectively.

Duration of Exposure for each drug RP6306 and FOLFIRI will be defined as the duration between the first and last doses of respective study drug

- Duration of RP6306 exposure = last dose date - first dose date + 1.
- Duration of FOLFIRI exposure = last infusion date - first infusion date + 14, due to 2 week infusion cycle

Overall duration of treatment for the study regimen is defined as Date of Treatment Discontinuation (from EOT page in the CRF) – first dose date +1. If treatment is still ongoing, use cut off date. If Date of Treatment Discontinuation is not collected, use the duration of exposure calculated above (take the longer of the either drugs)..

The last dose date will be obtained from the end of treatment (EOT) CRF page for each study drug. Number of days dosed will be derived as the number of days a patient received a dose of each study drug (i.e., excludes off treatment days and any missed doses).

Dose intensity for RP-6306 will be derived as:

Dose intensity = (total dose received/total planned dose)*100%

Total dose received (mg) for RP6306 is the sum of total doses (mg) received. If a patient had a dose reduction/change during treatment, then the total dose received will be calculated for each actual dose received and then summed to give the total dose received.

Total dose received: $\sum_{i=0}^{k}$ number of days dosed at dose $x_i * dose\ x_i$

for $i = 1$ to k where i represents the number of dose levels received and k = number of distinct dose levels

Total planned dose for RP6306 will be derived as initial assigned dose a patient will receivewithout any interruptions or reductions based on the time-period between the date of first dose and date of last dose after excluding days when dosing information is not available, accounting for the number of treatment days per week. This is assuming the days without dosing information is missing at random.

A dose interruption will be defined as a planned interruption where a decision is made to interrupt the dose temporarily, usually due to AE reason. Dose interruptions will be captured on the eCRF.

A dose reduction is any reduction prescribed by PI in dose/schedule compared to the initial dose.

Patients who do not have an end of treatment date in the eCRF at the time of analysis and reporting will be considered ongoing treatment. For deriving exposure, ongoing patients will be assumed to be ongoing at the date of the data cut off and therefore the data cutoff date will be used to derive exposure.

Exposure for RP6306 will be listed and summarized by the Safety Population and presented by module 1a and 1b and dose/schedule.

The following will be presented for RP-6306 (if applicable)

- Duration of exposure (days)
- Number and % of patients with at least 1 cycle, with at least 2 cycles...*etc (up to at least 5 cycles).*
- Number of cycles treated (completed)
- Total dose received (mg)
- Dose intensity based on initial planned dose (%)
- Number and % of patients with at least one dose interruption reported in dosing log by considering only those incidences when AE is indicated as a reason
  - Further broken down by number with 1, 2 or ≥ 3 interruptions
- Number and % of patients with at least one dose reduction (include dose reduction as a result of schedule change with less dose intensity) reported in dosing log considering only those incidences when AE is indicated as a reason
  - Further broken down by number with 1, 2 or ≥ 3 reductions
- Number of patients with any dose escalation per protocol

Patients with both an interruption and reduction will be included in both the interruption and reduction summaries.

The following will be presented for FOLFIRI.

- Duration of exposure (days)

- Number of infusions received

7.3. Laboratory Evaluations

All laboratory data recorded in the eCRF will be listed. Out-of-reference range values will be flagged as high (H) or low (L) in the listings. The results in standard unit will be used in the summary tables.

Box plots for percent changes from baseline over time for lab parameters will be produced by for all treated patients, based on the safety population and the number of patients with data at the relevant timepoints from selected lab tests. Sample size for each timepoint will be displayed. Summary tables of actual and change from baseline from all the numerical lab tests will be provided.

Selected laboratory assessments (hemoglobin, neutrophils, white blood cells [WBC], platelets, ALT, AST, BUN, total bilirubin, and creatinine) will be also presented in shift tables showing baseline grade vs. maximum grade on study for lab assessment with CTCAE grading, based on all post-baseline data including unscheduled assessments. The denominator for each on-treatment maximum grade is the total number of patients in the corresponding row for baseline grade (i.e., the baseline row totals). The shift from baseline to worst value will be summarized.

For lab assessments which do not have CTCAE grading these will be categorized as low/normal/high based on reference ranges and shifttables will present baseline versus worst value on study.

If worst criteria could be a low or a high value or an increase or decrease (i.e., in both directions) then shift tables should be split to show shift from baseline to worst low/decrease value and then repeated for worst high/increase value. For example, CTCAE grade criteria is given for both lymphocytes count increased and lymphocyte count decreased.

Table 3: Clinical Safety Laboratory Analytes from the Protocol

Hematology	Serum Chemistry	Urinalysis
• White blood cell count with differential (including at minimum: neutrophils, basophils, eosinophils, lymphocytes, monocytes) • RBC count • Hemoglobin • Hematocrit • Platelet count	• Albumin • Alkaline phosphatase • ALT • AST • BUN and/or urea • Calcium • Chloride • Creatinine • Glucose • Lactate dehydrogenase • Phosphate or phosphorus • Potassium • Sodium • Magnesium • Total bilirubin	• Specific gravity • Leukocyte esterase • Ketones • Protein • Glucose • Nitrite • Occult blood • Microscopy (if clinically indicated) • pH

Hematology	Serum Chemistry	Urinalysis
	• Direct bilirubin • Total protein • Uric acid	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen

Post-baseline liver function tests including unscheduled assessments will be summarized in the following categories in Safety Population. Corresponding listing will be produced to assess clinical relevance of these events (some maybe due to underlying disease):

- AST > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- ALT > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- ALP > 3 × ULN or 3 × Baseline (if baseline value is >ULN)
- Total bilirubin > 2 × ULN

7.4. Vital Signs and Abnormalities

Descriptive statistics of pulse/heart rate, blood pressure (systolic and diastolic) (sitting/semi- recumbent), weight, and body temperature values will be summarized at baseline and post baseline visits, and changes from baseline will be summarized for post baseline visits based on the Safety Population. A separate listing will include all the vital sign measurements, including those from the unscheduled visits.

The following post-baseline vital signs will be summarized based on the Safety Population:

- Maximum post-baseline in SBP:
  - No increase
  - Increase < 20 mmHg
  - Increase ≥ 20 mmHg
    - ≥ 160 mmHg and increase ≥ 20 mmHg
- Maximum post-baseline in DBP:
  - No increase
  - Increase < 20 mmHg
  - Increase ≥ 20 mmHg
    - ≥ 100 mmHg and increase ≥ 20 mmHg

For the number of subjects meeting each category for the post-baseline results or for the change from, the numerator is the number of subjects with meeting the criterion at any post-baseline including the unscheduled, and the denominator is the number of subjects with normal baseline and at least one post baseline assessment including unscheduled visits in the Safety Population.

A listing for patients with any post-baseline potentially clinically significant changes listed above will be also presented.

Box plots for percent changes from baseline over time will be produced by combining module 1a and 1b based on the Safety Population and the number of patients with data at the relevant timepoints.

7.5. 12-lead ECG

Descriptive statistics (n, mean, SD, median, minimum, and maximum) of ECG parameters,including PR interval, RR interval, QRS duration, QT interval, and QTcF interval (Fridericia's corrections) will be presented for baseline, eachpost-baseline visit, and change from baseline to each post baseline visit for Safety Population. All measurements, including those during unscheduled visits, will be provided in data listings, but only the scheduled measurements will be included in the by-visit summary. The average of triplicate 12-lead ECG results will be used for descriptive statistics.

Overall ECG interpretation category (normal, abnormal NCS (not clinically significant), abnormal CS (clinically significant), and not evaluable) is collected in the CRF at baseline and each scheduled post-baseline visit. Shifts in ECG interpretation at baseline to worst post baseline will be presented. For triplicate 12-lead ECG results collected at a visit, the average of triplicate 12-lead ECG results will be used as the interpretation at baseline as well as post-baseline.

The QTcF will be categorized into the following categories.

- QTc interval >450 msec and ≤480 msec
- QTc interval >480 msec and ≤500 msec
- QTc interval >500 msec

The change from baseline in QTcF will also be categorized separately as follows:

- QTc interval increases from baseline by >30 msec and ≤60 msec
- QTc interval increases from baseline by >60 msec

For the number of subjects meeting each category for the post-baseline results, the numerator is the number of subjects with meeting the criterion at any post-baseline including unscheduled visits and the denominator is the number of subjects with normal baseline and at least one post baseline assessment including unscheduled visits in the Safety Population. For the number of subjects meeting each category for the change at post-baseline from baseline, the numerator is the number of subjects with meeting the criterion at post-baseline and the denominator is the number of subjects with baseline and at least one post baseline assessment in the Safety Population.

Box plots for absolute and pchange from baseline for QTcF will be produced by combining module based on the Safety Population and the number of patients with data at the relevant timepoints. All ECG parameters will be listed in a data listing. All ECG tables and listings will be reported on the safety analysis set.

A separate analysis on correlation between exposure and QTc will be performed as part of the population PK/ER analysis (outside the scope of this SAP).

7.6. Physical Examination and ECOG Performance Status

Abnormalities identified from physical examination will be listed for the safety analysis set.

Shift table of baseline ECOG performance to worst post-baseline status will be summarized as the number and % of patients in each ECOG category based on the Safety Population.

Any change in PE findings assessed as clinically significant should be recorded as an AE or SAE.

8. EFFICACY DATA

The efficacy analysis will be summarized by dose combination. 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.

Efficacy data will be summarized using the Efficacy Population.

8.1. Derivation of Efficacy Endpoints

8.1.1. Best Percentage Change in Tumor Size

Best percentage change in tumor size is defined as the largest decrease or smallest increase (in the absence of a decrease) in the sum of diameters of the TLs prior to progression or last evaluable assessment in the absence of progression.

- If a patient receives another anti-cancer therapy prior to progression, then data up until the least evaluable TL assessment prior to the start of subsequent therapy will be included
- If a patient does not have any evaluable post-treatment TL assessments to allow a derivation of best percentage change from baseline, they will be excluded from analysis

8.1.2. Objective Response Rate (ORR)

Objective Response Rate (ORR) is defined as the proportion of patients with a confirmed response of CR or PR (i.e., 2 visit responses of either CR or PR at least 4 weeks apart) according to RECIST v1.1 criteria. This analysis will be limited to patients with measurable disease.

- Response will be assessed based on all evaluable assessments up to and including progression per RECIST v1.1. Responses occurring following subsequent anti-cancer therapy will be excluded from the assessment of ORR but will be included in the listing.

8.1.3. Best Overall Response Rate

Best Overall Response Rate is defined as the proportion of patients with confirmed or unconfirmed response of CR or PR based on best overall response by investigators across all visits. Unconfirmed CR or PR will be defined as those patients with CR or PR only reported once in overall tumor assessment form by the Investigators according to RECIST 1.1.

Note that the unconfirmed CR or PR (assessed by investigator) is added as a response criterion in addition to protocol defined confirmed CR or PR, to identify signal of anti-tumor activity for the treatment.

8.1.4. Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients with a best overall response of CR or PR according to RECIST v1.1 based on Investigator's assessment or duration on treatment of at least 16 weeks without evidence of progression.

CBR will be defined for patients in efficacy population only.

8.1.5. Duration of Response (DOR)

Duration of Response (DOR) will be derived for patients with a confirmed CR or PR only. DOR is defined as the time from the date of the earliest qualifying response (CR or PR) to the date of disease progression or death for any cause, whichever occurs earlier. Note, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint.

Given responses are required to be confirmed, the date of earliest qualifying response is the latest date for the visit where the initial overall visit assessment of CR/PR was observed rather than the confirmation visit assessment.

For patients who are alive without disease progression following response, DOR will be censored on the date of the last evaluable tumor assessment, last follow-up for disease progression, or data cut-off date, whichever occurs first. Handling of death without PD will be similar to PFS.

Table 4 gives the details rules of defining censoring/event for DOR.

Table 4: Censoring rule for Duration of Response (DOR) based on radiographical tumor assessment or death

Situation	Date of Censoring or Date of Event	DOR (weeks)	Censor
Documented disease progression (PD) before data cutoff date	Date of first PD	(Date of first PD – Date of first PR/CR + 1)/7	0
No PD, but death date before data cutoff date, or death date within 12 weeks after last adequate tumor assessment	Date of death	(Date of death – Date of first PR/CR + 1)/7	0
No PD and no death before data cutoff date, or death date beyond 12 weeks after last adequate tumor assessment	Date of last adequate tumor assessment[a] before data cutoff	(Date of last adequate tumor assessment[a] – Date of first PR/CR + 1)/7	1

[a] Adequate disease assessment is defined as a response assessment other than "not assessed" or "not evaluable."

8.1.6. Categorization of Best Tumor Response

For supportive information, the following confirmed best response categories will be derived for all patients with at least one post-baseline tumor assessment:

- Complete Response (CR): 2 visit responses of CR at least 4 weeks apart.
- Partial Response (PR): 2 visit responses of PR at least 4 weeks apart.

- Stable Disease (SD): If not confirmed CR/PR, at least one visit response of SD (or better i.e., unconfirmed CR/PR) recorded at least 6 weeks after the date of first dose of study drug.
  - To allow for the protocol window of ± 7 days, an overall assessment of SD on or after day 35 (i.e., 5 weeks) will be regarded as stable disease.
- Progressive Disease (PD): If not CR/PR/SD, and with at least one response of disease progression
- Not-Evaluable (NE): No evidence of CR, PR, SD, or PD. Either by default or the only visit response recorded is 'NE'.

8.1.7. Change in Tumor Size

The percent change in target lesions (TL) size compared to baseline will be derived at each visit as:

- Percent change in TL at Visit X = [(Visit X TL sum of diameters – Baseline TL sum of diameters)/Baseline TL sum of diameters] *100

The best percent change will be derived as the largest decrease or smallest increase (in the absenceof a decrease) up to and including progression or last evaluable assessment in the absence of progression. If a patient receives another anti-cancer therapy prior to progression, then data up until the last evaluable TL assessment prior to the start of subsequent therapy will be included.

Note that only TLs matched with baseline will be used for calculation of percent change.

8.1.8. Progression Free Survival (PFS)

Progression-Free Survival (PFS) is defined as the time from the first day of study drug administration (Day 1) to disease progression as defined by RECIST v1.1 criteria or death from any cause.

TL, NTL and new lesion assessments may be performed on different dates. The following rules will be applied for determine progression and censoring dates:

Date of progression will be determined based on the earliest of the dates of the component that triggered the progression. For example, if progression was due to a new lesion only then the date of the new lesions would be used. If progression was due to TLs and a new lesion, then the earliest of the TL and new lesion dates would be used.

Patients who are alive and free from disease progression will be censored at the date of their last evaluable tumor assessment prior to or equal to the data cut off date.

Any patient who dies in the absence of progression after 2 or more missed assessments will be censored at the date of their last radiographic tumor assessment. Specifically, if the death date is >12 weeks from the last tumor assessment, the death date will not be used for the calculation of PFS.

If a patient has no baseline tumor assessment/no post dose tumor assessments then they will be censored at 0 days for PFS, unless they died within 12 weeks from the date of first dose (and also before cut-off), in which case their death date will be used as a PFS event.

Table 5 gives the details rules of defining censoring/event for PFS.

PFS at 6 months will be reported based on KM methods as the number and % of patients estimated to be progression free at 6 months.

Table 5: Censoring Rule for time-to-event analyses (PFS) based on radiographical tumor assessment or death

Situation	Date of Censoring or Date of Event	Censor
Documented disease progression (PD) before data cutoff	Date of first PD	0
No PD, but death date is within **12** weeks from the last adequate post-baseline assessment[a]	Date of death	0
No PD, no post-baseline assessment, and death date is within 12 weeks from the date of first dose	Date of death	0
No PD, no post-baseline assessment[a], and death date > **12** weeks from the date of first dose	Date of the first dose	1
No PD, no post-baseline assessment[a], and no death	Date of the first dose	1
No PD, Death date > 12 weeks from the last adequate post-baseline assessment[a] (e.g., 2 or more consecutive missed scheduled disease status assessments and the gap > **12** weeks)	Date of last adequate tumor assessment[a]	1
No PD or death, but with last adequate assessment[a] before data cut off	Date of last adequate tumor assessment[a]	1

[a] Adequate disease assessment is defined as a response assessment other than "not assessed" or "not evaluable."

This Censoring Rule is used for the data after implementation of data cut off.

8.2. Efficacy Analysis Methods

For overall response rate, ORR, and CBR, the number and percentage of patients along with an exact binomial 95% confidence interval (CI), using the Clopper-Pearson method, will be presented.

In general, summary of all efficacy endpoints will be provided by dose level separately for Module 1a and 1b patients.

The assessment of tumor efficacy will be based on the measurements recorded by the investigator.

A summary of the best objective response will be presented which will include the number and percentage of patients with a best response of CR, PR, SD, PD and NE.

Time-to-event endpoints (PFS) will be analyzed using the KM method and results will be summarized by the 25th, 50th and 75th percentiles, if estimable, with associated 2-sided 95% CIs. KM plots will be provided. For PFS, the number (%) of patients with an event and the number (%) of patients censored will also be presented. The rate of PFS at 16 weeks and 24 weeks will be derived from the corresponding Kaplan-Meier curves. The KM analyses for DOR may be replaced by descriptive summary of median, and quartiles with individual listing for responders if total confirmed responders are few and less than 5 patients.

Maximum reduction in tumor size will be summarized by n, mean, standard deviation, median, 25th quartile and 75th quartile, minimum and maximum. The spider plots displaying change in tumor size over time for each patient will also be provided for each module and dose/schedule group as described above.

In addition, waterfall plots showing the best percentage change from baseline (largest decrease or smallest increase in the absence of a decrease) in the sum of the TL sizes will be produced for each module by dose/schedule group indicating each patient' best objective response.

Swimmer plots will be produced for each module and dose/schedule group to show the duration of study treatment per patient with indicators for timing of response, progression or death, where applicable.

9. PHARMACOKINETIC (PK) PARAMETERS DATA

All PK data will be presented based on the Pharmacokinetic Population and presented by module 1a or 1b and dose/schedule.

PK parameters for RP-6306, irinotecan and SN-38 will be calculated using noncompartmental analysis (NCA) or population PK modeling. In summaries of raw concentration data, plasma concentration that falls below the lower limit of quantitation (BLQ) will be treated as zero in data tabulation. In individual PK parameter estimation, BLQ plasma concentrations will be treated as zero if the value preceded T_{max}. BLQ plasma concentrations will be treated as missing if the value occurs after T_{max}. All BLQ concentration values will be listed as reported.

PK concentrations and parameters will be listed for all patients in the PK population.

Individual patient and mean plasma concentration-time profiles will be plotted on linear and semi-logarithmic scales for each cohort and dose/schedule.

The following summary statistics will be presented for $AUC_{0\text{-}last}$, C_{max}, T_{max}, terminal elimination rate constant (Kel), and terminal elimination half-life (t½) for RP-6306, irinotecan and SN-38. $AUC_{0\text{-}8h}$, $AUC_{0\text{-}24h}$ (for QD dosing), $AUC_{0\text{-}12h}$ (for BID dosing) will be calculated for RP-6306 only. Other parameters maybe calculated to support the development of RP-6306. The PK parameters will be calculated using Phoenix WinNonlin version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or other

appropriate software as appropriate. Default reporting in text and tables is 3 significant figures except for time related parameters ($t_{1/2}$, and T_{max}). Time related parameters will be reported to two decimal places.

PK parameters for RP-6306, irinotecan and SN-38 will be derived using non-compartmental methods from the concentration--time profiles as follows:

Table 6: Derivation of Pharmacokinetic Parameters Prior to Analysis

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration within the dosing interval	Observed directly from data
t_{max}	Time to C_{max}	Observed directly from data as time of first occurrence
$AUC_{0\text{-}last}$	Area under the plasma concentration-time curve from time 0 to t ("t" being the longest time interval evaluable in all periods)	Linear up/Log down method
$AUC_{0\text{-}8h}$	Area under the plasma concentration-time curve from time 0 to 8 hours post dose	Linear up/Log down trapezoidal method
$AUC_{0\text{-}12h}$	Area under the plasma concentration-time curve from time 0 to 12 hours post dose	Linear up/Log down trapezoidal method
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time 0 to 24 hours post dose	Linear up/Log down trapezoidal method
$t_{½}$	Elimination half-life	Ln (2)/k_{el}, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve

PK parameters will not be calculated for profiles with less than three quantifiable concentrations. Actual PK sampling times will be used in the derivation of PK parameters.

For PK parameters on the respective cycles and days appropriate to a given dose and schedule, the following will be calculated:

- The geometric mean (gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale).
- Coefficient of variation (CV, calculated as CV =100*SD/mean], where SD is the standard deviation of the untransformed data).]).
- Geometric Coefficient of Variation calculated using log transformed data (Geom CV)
- Arithmetic mean calculated using untransformed data.
- Standard Deviation (SD) calculated using untransformed data.
- Minimum.
- Median.
- Maximum.
- Number of observations (n).

T_{max} will be summarized as median, minimum, maximum and number of observations (n). -For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual patient plots by time, the actual PK sampling time will be used.

Given that no formal hypothesis testing is being undertaken for this module, no statistical inference will be made.

9.1. Population PK/PD Modelling

The population PK/PD and exposure-response analyses will be developed and reported separately from the CSR. Exploratory analysis of the population PK and biomarker changes may also be performed and also reported separately from the CSR. In addition, population PK and PK/PD modelling will be addressed outside of the SAP.

11. INTERIM ANALYSIS

No interim analysis is planned for this study.

12. REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, Schwart LH, Ford R, Dancey J, Arbuck S, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2):228-47.

Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. Appl Statist. 2015;64(3):507-523.

Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. Clin Cancer Res. 2016;22(17):4291-301

APPENDIX 1. DEFINITION OF DOSE LIMITING TOXICITY (DLT)

DLTs are defined as follows:

Hematologic AEs:

- Grade 4 neutropenia lasting at least 7 days or if G-CSF or GM-CSF is given at any time
- Febrile neutropenia (defined as absolute neutrophil count [ANC] < 1000/ mm^3 with a single temperature of ≥38.3°C[101°F] or a sustained temperature of ≥38°C[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.

Non-hematologic AEs:

• 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

The following events will not be considered a DLT:

- 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

APPENDIX 2. GYNECOLOGICAL CANCER INTERGROUP DEFINITIONS FOR RESPONSE AND PROGRESSION IN PATIENTS WITH OVARIAN CANCER

For patients with ovarian cancer with elevated CA-125 levels, response evaluation will include cancer antigen 125 (CA-125) in addition to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria as per Gynecological Cancer Intergroup (GCIG) criteria [Rustin 2011].

Definition of Response by CA-125

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

Definition of Progression by CA-125

- For patients with elevated CA-125 pre-treatment that normalizes or for patients with CA-125 in the normal range at baseline: CA-125 at least 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.
- For patients with elevated CA-125 pre-treatment which never normalizes: CA-125 at least 2 times the nadir value on 2 occasions at least 1 week apart.
- Progressive disease (PD) by objective change in tumor size should always take precedence over changes in CA-125 should it occur first. If measurable disease is reducing in size but the CA-125 suggests progression the patient should remain on treatment.
- CA-125 progression will be assigned the date of the first measurement that meets the above criteria.

Note: CA-125 progression in the absence of radiographic or other clinical evidence of progression will not be sufficient criteria for treatment discontinuation in this study.

Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days.

Evaluation of Best Overall Response by Combined CA-125 and RECIST 1.1 Criteria

- If patients have a CA-125 response but have PD by RECIST within 28 days of the CA-125 response, they will be classified as PD.
- Patients whose best response by RECIST is stable disease (SD) but who have a CA-125 response will be classified as CA-125 responders

- For a patient to be classified as a complete responder according to RECIST, CA-125 levels must be within the normal range

For Patient with Measurable Disease

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

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

For Patients without Measurable Disease

CA 125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-PD	No	PR	
Normalized but no response	Non-CR/Non-PD	No	SD	
Non-PR/non-PD	Non-PD	No	SD	
PD	Any	Yes or No	PD	
Any	PD†	Yes or No	PD	
Any	Any	Yes	PD	

*Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
†Unequivocal progression in nontarget lesions may be accepted as disease progression.
CR, Complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS, VERSION 1.1

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once 8 wks. from first dose of study medication**
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion (Eisenhauer 2009).

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

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

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

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

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

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

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2): 228–247.