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Statistical Analysis Plan 2

A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal and Genitourinary Tumors

PCYC-1128-CA

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Version 1.0

STATISTICAL ANALYSIS PLAN (SAP) APPROVAL

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By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ATC	anatomical therapeutic chemical
CEA	carcinoembryonic antigen
CR	complete response
CSR	clinical study report
CRC	colorectal adenocarcinoma
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLRC	dose level review committee
DLT	dose limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
GC	gastric carcinoma
IA	interim analysis
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
RCC	renal cell carcinoma
RP2D	recommended Phase 2 dose
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
TE	treatment-emergent
TEAE	treatment-emergent adverse event
UC	urothelial carcinoma

1. INTRODUCTION

This statistical analysis plan (SAP) is based on protocol Amendment 2.1 and is to define key elements including variable definitions, and statistical methods for analysis of data in evaluation of efficacy and safety of the study PCYC-1128-CA. Analyses of biomarkers and pharmacokinetics are not in scope of this document. Throughout this SAP, "study treatment" and "study drug" are used interchangeably, both refer to any of the study drugs including ibrutinib or the companion drug for the combination therapy and ibrutinib for the single-agent therapy..

Analysis methods specified in this document take precedence over those described in the protocol should there be any difference. Any changes from the protocol will be documented in Section 6, Changes in Protocol Planned Analysis.

There are two clinical study reports (CSRs) for this study. CSR #1 is for RCC Cohort 1, GC Cohort 3, and CRC Cohort 4 and was finalized on 10 Nov 2020. CSR #2 is for all UC cohorts (Cohorts 2, 5, and 6), and will also contain updated analyses for Cohorts 1, 3, and 4. Database extraction will take place after last patient has exited study and necessary cleaning activities have been completed, currently anticipated in the third quarter of 2021 to prepare for CSR #2. This SAP (referred to as SAP2) is to cover the analysis plan for Cohorts 2, 5 and 6 in CSR #2. A previous SAP (referred to as SAP1) was written to cover the analysis plan for CSR #1. The updated analyses for Cohorts 1, 3 and 4 that will be included in CSR #2 will be performed in the same manner as described in SAP1.

1.1. Study Design

This is an open-label, Phase 1b/2 multi-center study to assess the safety and efficacy of ibrutinib monotherapy (Cohort 5) in subjects with previously-treated urothelial carcinoma (UC) and ibrutinib combination therapy (Cohorts 1-4, 6) in subjects with previously treated renal clear cell carcinoma (RCC), urothelial transitional cell carcinoma (UC), gastric or gastroesophageal junctional adenocarcinoma (GC), and NRAS/KRAS wild-type colorectal adenocarcinoma (CRC) as listed below. Each cohort in this study will assess a different malignancy and/or anticancer agent in combination with ibrutinib or single-agent ibrutinib and follow an independent and parallel design:

• Metastatic RCC (Cohort 1) minimum of 1 and maximum of 4 prior regimens, one or more of which must have included a VEGF-TKI. Treatment with ibrutinib + everolimus.

• Advanced (locally recurrent inoperable and/or metastatic) UC (Cohorts 2, 5, 6)

Cohort 2: Minimum of 1 and maximum of 2 prior regimens, one of which must have included a platinum-based regimen. Treatment with ibrutinib + paclitaxel.

Cohort 5: Minimum of 1 and maximum of 2 prior regimens, one of which must have included a checkpoint inhibitor. Treatment with single agent ibrutinib.

Cohort 6: **EITHER**: not eligible for cisplatin chemo with a PDL-1score (CPS) of ≥ 10 without prior treatment, **OR** progressed on platinum chemo or within 12 months of neo- or adjuvant therapy with a platinum chemotherapy. A minimum of 1 and maximum of 2 prior therapies. Treatment with ibrutinib + pembrolizumab.

• Advanced (locally recurrent inoperable and/or metastatic) GC (Cohort 3) minimum of 1 and maximum of 3 prior regimens one of which must have included a fluoropyrimidine regimen. Treatment with ibrutinib + docetaxel.

• Metastatic CRC (Cohort 4) minimum of 2 and maximum of 4 prior regimens, which must have included both an irinotecan and an oxaliplatin based regimen unless unable to tolerate irinotecan chemotherapy. Treatment with ibrutinib + cetuximab.

This Phase 1b/2 study is divided into 2 parts. An initial Phase 1b portion will evaluate the safety and tolerability of single-agent ibrutinib and ibrutinib in combination with each anticancer agent to assess any dose limiting toxicity in order to determine the recommended Phase 2 dose (RP2D) for each cohort.

The Phase 2 portion will assess primary endpoints of progression-free survival (PFS) (with an incorporated interim analysis) for RCC and UC Cohort 2, and overall response rate (ORR) using a Simon's minimax 2-stage design for GC, CRC, and UC Cohorts 5 and 6.

Phase 1b

The Phase 1b portion of this study is performed independently in six separate cohorts defined by the clinical indication; RCC, UC, GC, and CRC.

For cohorts 1-4, safety and dose-limiting toxicity (DLT) assessment will be evaluated in 3-9 subjects at each dose level in a 3+3+3 design. At each dose level, DLT assessment will be performed in the first 3 subjects. If 1 of 3 subjects experiences a DLT during the first treatment cycle, the same dose level will be expanded to 6 subjects, and if 2 of the 6 experience a DLT, the same dose level will be expanded to 9 subjects. At the 560 mg/day dose level (DL 1), if 0 out of 3, 1 out of 6 or 2 out of 9 subjects (≤ 22%) experience a DLT during the first treatment cycle, dose escalation to 840 mg/day (DL 2) will occur. At DL 1 (560 mg/day), if ≥ 33% of subjects experience a DLT (e.g., > 2 out of 6 or > 2 out of 9 subjects), the dose will be de-escalated to 420 mg/day (dose level minus one; DL -1). At the 840 mg/day dose level (DL 2) cohort, subjects will be enrolled in a similar fashion.

For UC cohort 5, the single-agent dose of 840 mg will be confirmed and documented in the first 6 patients; safety data will be described.

For UC Cohort 6, a 6+3 dose de-escalation design will be implemented. For the Phase 1b portion of Cohort 6, if 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6 subjects experience a DLT, dose de-escalation will occur and additional 6 evaluable subjects will be enrolled. If the incidence of DLTs during the DLT observation period is <33.3% (i.e., ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2 and will be defined as the RP2D.

The RP2D will be determined when 6–9 subjects at the dose level complete the DLT observation period based on the totality of the data including dose reductions (of both ibrutinib and/or the combination therapy), treatment-limiting toxicities (outside of DLTs), the available pharmacokinetic data and the toxicity profile obtained during Phase 1b. In order to determine the RP2D dose level, a minimum of 6 DLT-evaluable subjects will be required at the RP2D dose level who are defined to have completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent, after the initiation of therapy at the start of Cycle 1.

For UC Cohorts 5 and 6, a DLT-evaluable subject will have ≥ 90% compliance with ibrutinib during Cycle 1 (the first 21 days). At each dose level, the decision of de-escalation will be made with at least 6 DLT-evaluable subjects. However, if at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped.

For combination therapy of ibrutinib and other anticancer agent specified below, the starting dose of ibrutinib will be 560 mg daily in the following 5 cohorts: RCC Cohort 1: ibrutinib + everolimus, UC Cohort 2: ibrutinib + paclitaxel, GC Cohort 3: ibrutinib + docetaxel, CRC Cohort 4: ibrutinib + cetuximab, UC Cohort 6: ibrutinib + pembrolizumab.

For single-agent ibrutinib, the starting dose will be 840 mg: UC Cohort 5: single-agent ibrutinib.

A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort to determine the RP2D, prior to continuing with enrollment into the Phase 2 portion (enrollment may not be held for UC Cohort 5 as safety data is available for more than 40 subjects for ibrutinib 840 mg in combination with paclitaxel data). The DLRC will review the safety data in the first 6 evaluable subjects enrolled in Cohort 5 to confirm 840 as the single-agent dose. Members of this committee will include the Medical Monitor or designee, a drug safety representative, a biostatistician, and at least 2 participating investigators/designees.

Any Phase 1b subjects who discontinue one or more study drugs, or require dose reduction within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced, unless the discontinuation is in association with a DLT. Subjects who miss one or more scheduled doses (more than 2 doses for UC cohorts 5 and 6) of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will continue. However, such a subject will not be evaluable for DLT assessment and will be replaced for DLT assessment purposes.

After the RP2D has been defined for each cohort, enrollment in Phase 2 will commence in that cohort.

Phase 2

For each cohort in the study, a separate analysis will be performed to evaluate its response and safety profile.

Subjects treated at RP2D in Phase 1b will be included in the Phase 2 analyses.

In all cohorts, subjects who are dosed at the RP2D level and withdraw prior to the completion of at least 2 cycles of study treatment, for reasons other than unacceptable toxicity or disease progression, may be replaced after consultation with the Sponsor.

For GC (Cohort 3), CRC (Cohort 4), and UC Cohorts 5 and 6, if a subject in Simon's Stage-1 discontinues prior to the first tumor response assessment for reasons other than disease progression, the subject may be replaced. Enrollment may continue into Stage-2, whilst the response evaluation and analysis from the Stage-1 are completed. If the number of responders observed among the evaluable subjects in Stage-1 is less than the number of responders required to proceed per the Simon's 2-stage design, the relevant cohort may be terminated for futility.

1.2. Endpoints

The rest of this SAP2 document describes endpoints and analysis relevant to CSR #2. Updated analyses from CSR #1 (Cohorts 1, 3, and 4) will be performed in the same manner described in SAP1, based on updated data extraction.

1.2.1. Primary Endpoint

Phase 1b

- To determine the RP2D of ibrutinib in combination with paclitaxel (Cohort 2) and pembrolizumab (Cohort 6) in UC, confirm the RP2D of single-agent ibrutinib in UC Cohort 5 and assess DLTs during the 21-day DLT assessment period.

Phase 2

- Progression-free survival (PFS) in accordance with RECIST 1.1 criteria in UC Cohort 2
- Overall response rate (ORR) in accordance with RECIST 1.1 criteria of ibrutinib as single agent in UC Cohort 5 and ibrutinib combination therapy in UC Cohort 6

1.2.2. Secondary Endpoints

Phase 1b

- Secondary endpoints are to assess ORR and disease control rate (DCR) in each cohort. ORR is defined as the proportion of patients who have a best response of partial response (PR) or complete response (CR) to therapy. DCR is the proportion of patients who have a best response of PR, CR, or stable disease (SD).

Phase 2

- Disease control rate (DCR) in all cohorts
- PFS in UC Cohorts 5 and 6
- ORR in UC Cohort 2
- Overall survival (OS) in all cohorts
- Duration of response (DOR) in all cohorts

1.2.3. Safety Assessments

Phase 1b

- To assess the safety and tolerability of ibrutinib in each cohort

Phase 2

- Safety and tolerability of ibrutinib combination therapy in each cohort

1.2.4. Exploratory Endpoints (Phase 2)

- [redacted]

1.3. Statistical Hypotheses

For each cohort, the design will provide approximately 80% power to perform one-sided hypothesis testing at an α level of 0.05.

Cohort	Hypothesis Testing
UC Cohort 2	H_0: $m \leq 2.3$ months versus H_1: $m \geq 4.1$ months, where m is the median PFS.
UC Cohort 5	H_0: $\pi \leq 5\%$ versus H_1: $\pi \geq 20\%$, where π is the overall response rate.
UC Cohort 6	H_0: $\pi \leq 20\%$ versus H_1: $\pi \geq 35\%$, where π is the overall response rate.

H_0 is the null hypothesis. H_1 is the alternative hypothesis.

1.4. Sample Size Determination

The number of subjects required to be treated with ibrutinib at the RP2D level for the efficacy evaluation is determined for each disease cohort using the following methods.

UC Cohort 2

The primary endpoint for UC cohort 2 is median PFS. A sample size of approximately 55 efficacy evaluable subjects will provide 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS $\leq$ 2.3 months versus the alternative hypothesis median PFS $\geq$ 4.1 months. The median PFS for paclitaxel is assumed to be 2.3 months under the null hypothesis. The study is designed to detect a 78% increase in median PFS to 4.1 months for ibrutinib in combination with paclitaxel. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve at a minimum of 80% power is determined by a simulation method with an enrollment rate of 5 subjects per month and with the data cut time for analysis to be at 6 months following the last subject enrollment.

UC Cohort 5

The primary endpoint is ORR for this cohort. A total of up to 27 subjects treated with single-agent ibrutinib are to be enrolled based on Simon's 2-stage design. In Stage-1, 13 subjects will be enrolled and if at least one responder is observed, an additional 14 subjects will be enrolled in Stage-2. At the end of the study, if there are 4 or more responders, the null hypothesis will be rejected, and the study treatment would be considered acceptable for further clinical development.

This Simon's 2-stage minimax design would provide 80% power to test the historical response rate of 5% (null hypothesis) against the target response rate of 20% (alternative hypothesis) at a 1-sided significance level of 0.05.

UC Cohort 6

The primary endpoint is ORR for this cohort. A total of up to 53 subjects are to be enrolled based on Simon's 2-stage design. In Stage-1, 31 subjects will be enrolled and if at least 7 responders are observed, an additional 22 subjects will be enrolled in Stage-2. At the end of the study, if there are a minimum of 16 or more responders, the null hypothesis may be rejected and the study treatment may be considered acceptable for further clinical development.

This Simon's 2-stage minimax design would provide 80% power to test the pembrolizumab response rate of 20% (null hypothesis) against the target response rate of 35% (alternative hypothesis) at a 1-sided significance level of 0.05.

Table 1 provides a summary for number of subjects needed in Stage 1 and Stage 2 of Simon's 2-stage design for UC Cohorts 5 and 6 in order to declare success.

Table 1: Number of Subjects and Number of Responders for Simon's 2-stage Minimax Design

Cohort (Total Number of Subjects)	Number of Subjects for Stage 1	Number of Responders in Stage 1 Needed to proceed to Stage 2	Number of Subjects for Stage 2	Number of Responders Need to Reject the Null Hypothesis for the Study
UC Cohort 5 (N=27)	13	≥ 1	14	≥ 4
UC Cohort 6 (N=53)	31	≥ 7	22	≥ 16

1.5. Planned Analysis

1.5.1. Phase 1b analysis

Analysis for Phase 1b will be conducted separately for each disease cohort and dose level when appropriate.

1.5.2. Interim Analysis (IA)

An interim analysis will be conducted for each cohort independently for the Efficacy Evaluable Population. UC Cohorts 5 and 6 were based on Simon's 2-stage design and the interim analysis stopping rule was determined by the design. For UC Cohort 2, interim analysis timing is when approximately 25 efficacy evaluable subjects dosed at the RP2D level have completed 4 months of follow-up. Details are provided below. Enrollment may continue while the interim analysis is being performed for each cohort. The analysis will be conducted on subjects who received RP2D from Phase 1b and Phase 2.

Go/No Go decisions at the time of the interim analyses will include all available clinical and safety data for that cohort and are not based solely on the efficacy data for the endpoint involved in the interim analysis. No multiplicity adjustment will be made for Cohort 2 final efficacy analysis.

UC Cohort 2

PFS is the primary efficacy endpoint for this cohort. A single interim analysis for futility will take place after approximately 25 efficacy evaluable subjects dosed at the RP2D level have completed 4 months of follow-up. The proportion of subjects that are PFS event-free at 4 months

will be assessed along with other safety and efficacy data in making the determination if the study should continue. Point estimator and 2-sided 90% Brookmeyer-Crowley confidence interval with log-log-transformed Greenwood variance estimate of the median PFS (mPFS) will be calculated to assess efficacy.

UC Cohorts 5 and 6

For those two cohorts, ORR is the primary endpoint and Simon's 2-stage minimax design is implemented to evaluate ORR following the Stage-1 boundaries in Table 1.

At the interim analysis of the Stage-1, the proportion of responding subjects (best response of CR or PR) will be calculated, along with other safety and efficacy data when making the determination if the study should continue into the Stage-2. Confirmation of response is not required for the interim analysis.

1.5.3. Final Analysis

The final analysis will be conducted after all efficacy evaluable subjects have completed a minimum period of follow-up for the primary endpoint or other key endpoint(s), or after all patients have exited the study.

There are two CSRs for this study. CSR #2 is for all UC cohorts (Cohorts 2, 5 and 6) and is covered in SAP2.

1.5.4. Blinding and Randomization Methods

Not Applicable. This is an open-label non-randomized study.

2. GENERAL ANALYSIS CONSIDERATION

Phase 1b

Data summary and data analysis will be conducted for each disease cohort separately. Data will not be pooled across disease cohorts or tested between disease cohorts.

Limited tables and listings will be generated, constituting a subset of the Phase 2 outputs, and include: baseline demographic, baseline characteristics, disease characteristics, treatment and study disposition, study drug exposure, DLTs, ORR, DCR, overview of treatment emergent adverse events (TEAEs), TEAEs by Systems Organ Class/Preferred Term/maximum severity, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to ibrutinib discontinuation. No subgroup will be summarized for this phase. Data will be summarized separately for each cohort by dose.

Phase 2

Data summary and data analysis will be conducted for each disease cohort separately. Data will not be pooled across disease cohorts or tested between disease cohorts.

Baseline, demographics, disposition, and safety data will be summarized by dose level (RP2D). Efficacy analysis will only be conducted for subjects treated at R2PD. Subjects who were treated with ibrutinib at the R2PD level in Phase 1b or Phase 2 will be combined in the summary.

Subgroup analyses may be undertaken to evaluate potential efficacy and/or safety trends and to assess internal consistency of any apparent treatment benefit. The subgroups for these cohorts will be determined by the level of clinical interest/relevance. Statistical hypothesis testing will not be performed for the subgroup analyses.

General Definitions:

For disease cohorts with a combination treatment, date of first dose of study treatment is defined as the date the subject received the first dose of ibrutinib or the companion drug (whichever occurs first) and date of last dose of study treatment is defined as the date the subject receive the last dose of ibrutinib or the companion drug (whichever occurs later).

Baseline value is defined as the last non-missing valid value collected prior to the first administration of study treatment. For subjects who have been enrolled but not treated, enrollment date will be used as the reference date for baseline if needed.

2.1. Analysis Sets

DLT Evaluable Population: Defined as subjects from Phase 1b who completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent after the initiation

of study treatment at the start of Cycle 1, or those who discontinued from study treatment due to a DLT event prior to completion of DLT observation period. The DLT Evaluable Population will be used for DLT assessments. Per protocol, subjects in Cohort 2 who miss one or more scheduled doses of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will continue. However, such a subject will not be evaluable for DLT assessment and will be replaced for DLT assessment purposes. For Cohorts 5 and 6, subjects may miss up to 2 doses of ibrutinib within 21 days after the initiation of therapy and still be evaluable for DLT assessment.

All Enrolled Population: Defined as all eligible subjects enrolled in the study.

All Treated Population: Defined as all subjects who received at least 1 dose of study treatment (ibrutinib or the companion drug for the combination therapy and ibrutinib for the single-agent therapy). This population is the same as the Safety Population defined in the protocol. For the purpose of analysis and CSR, All Treated Population will be used as the data set to summarize all the data unless otherwise indicated. Sensitivity analysis of efficacy endpoints will be performed based on this population.

Efficacy Evaluable Population: This population will be used to perform the primary analysis for the efficacy endpoint(s) and is defined as eligible (meet **all** of the inclusion and **none** of the exclusion criteria) subjects who received at least one dose of ibrutinib (at RP2D) in combination with at least one dose of the relevant companion drug or ibrutinib (at RP2D) for the single-agent therapy and fulfil the following criteria:

<u>UC Cohort 2 (PFS as the primary endpoint)</u>

1) Had at least one adequate post-baseline overall disease assessment per RECIST 1.1 guidelines or died prior to the first adequate post-baseline overall disease assessment.

<u>UC Cohorts 5 and 6 (ORR as the primary endpoint)</u>

1) Had measurable disease (i.e. at least one target lesion as defined in the protocol) per RECIST 1.1 guidelines at baseline.

2) Had at least one adequate post-baseline overall disease assessment per RECIST 1.1 guidelines.

2.2. Definition of Subgroups

Subgroup analyses will be performed for the selected variables in an exploratory fashion. Further clinically relevant and biomarker subgroups will be assessed if appropriate. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

Otherwise subgroup analysis will not be carried out if the distribution for the subgroup variable does not warrant the analysis.

Table 2: Baseline Subgroup Definition

Subgroup	Definition of Subgroup	Analysis Type
ECOG Performance status	0 *v* 1	E
Renal function (creatinine clearance)	< 60, ≥ 60 mL/min	E
Hepatic function (NCI ODWG definition)	normal, mild, moderate, severe (or normal vs. non-normal as appropriate)	E
Neutrophil;lymphocyte ratio	>3 *v* ≤3	E
Hemoglobin <10mg/dL	<10 *v* ≥10	E
Bellmunt prognostic risk factors	0, 1, 2, 3	E
Liver metastasis	Present, absent	E
Number of prior lines of therapy	0 (Cohort 6 only), 1,2,3,4	E

Analysis type: E = Efficacy – Primary endpoint only (PFS or ORR).

3. SUBJECT INFORMATION

Subject information will be summarized descriptively by ibrutinib dose level (RP2D versus other dose level) for each disease cohort individually. Subjects who were treated with ibrutinib at the R2PD level in Phase 1b or Phase 2 will be combined in the summary.

3.1. Subject Disposition

The disposition tables will include the following summaries:

- Analysis populations (all enrolled subjects)
- Enrollment by country and investigator/site (all enrolled subjects)
- Study treatment disposition, study treatment duration and discontinuation of study treatment (All Treated Population)
- Study status and study exit for all enrolled subjects.

Time on study is defined in the same way as overall survival with reversed censoring, i.e., subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

3.2. Demographics, Baseline Characteristics, and Baseline Disease Characteristics

Subject demographics and baseline characteristics will be summarized with descriptive statistics for the All Treated Population by cohort.

3.3. Prior and Concomitant Medications

Medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class according to World Health Organization drug dictionary.

Prior medications are defined as medications that started prior to the first dose of study treatment. Concomitant medications are defined as medications that were taken on treatment (i.e. from the date of first dose of study treatment through the date of last dose of study treatment).

Concomitant medications will be summarized by ATC class and preferred term (PT) based on All Treated Population for each disease cohort. Each subject will be counted once only for overall, each PT, and each ATC class. The following concomitant medications will be summarized separately:

- CYP3A inhibitors and inducers – This list requires a medical review, with finalization at the time of analysis
- Anticoagulants and antiplatelet agents will need medical review, with finalization at the time of analysis

3.4. Extent of Exposure to Study Treatment

For each disease cohort, exposure to study treatment will be summarized for each study drug for the All Treated Population. Descriptive statistics will be provided, by study drug, for the followings: treatment duration (month), total number of doses received, total number of cycles received (for chemotherapy), total cumulative dose administered, dose intensity and relative dose intensity (%), and number (%) of subjects with dose reduction due to adverse events (AEs), dose delay due to AEs and dose reduction or delay due to AEs.

3.5. Prior Anti-cancer Treatments and Subsequent Anti-cancer Treatment

Anti-cancer treatment includes drug therapies, radiation, and surgeries and procedures performed with therapeutic intent. The ATC level of anti-cancer drug therapies will be specified in the mock-up table footnote. Prior anti-cancer treatments are treatments received prior to study treatment. Subsequent anti-cancer treatment are treatments received after date of last dose of study treatment. Prior and subsequent anti-cancer treatment will be summarized separately using All Treated population for each disease cohort.

3.6. Visit Impact of Logistical Restriction Due to COVID-19

Visit and assessment impacts of logistical restrictions due to the COVID-19 pandemic will be summarized by the type of impact (missed visit, in person/partial assessment done, and virtual visit/phone call) recorded on the Visit Impact CRP page for each treatment arm.

Information for treatment discontinuation and study exit during the COVID-19 pandemic will be listed.

4. ANALYSIS FOR EFFICACY ENDPOINTS

For Phase 1b, data will be summarized by dose level for each cohort separately. As described in Sections 1.5 and 2, limited tables and listings will be included. Descriptive summaries will be provided, and confidence intervals described in Table 4 for ORR, DCR can be applied as data warrant. No subgroup will be summarized for this phase.

For Phase 2, efficacy and safety data will be summarized for each disease cohort separately. All subjects treated at the RP2D dose level of ibrutinib in Phase 2 or Phase 1b will be analyzed together). Hereafter this will be referred to as "Phase 1b/2 RP2D" in the tables.

Primary analysis of each efficacy endpoint will be performed using the Efficacy Evaluable Population at the time of final analysis, unless otherwise indicated. Sensitivity analyses will be performed for some efficacy endpoints using the All Treated Population. Safety data will be summarized using the All Treated Population.

Efficacy analyses will be based on the overall disease assessments determined by the investigator per RECIST 1.1 guidelines. Efficacy endpoint definitions and analysis methods for Phase 2 are described in Table 4.

Table 3: Summary of Efficacy Analyses

Endpoint	Definition	Analysis Methods
Primary Endpoint (UC Cohort 2)		
PFS	Time from the date of first dose of study treatment to the date of first documentation of progressive disease (PD) or date of death from any cause, whichever occurs first, regardless of the use of subsequent anti-cancer treatment. Subjects who were not known to have disease progression or death at the data extraction will be censored at date of last adequate post-baseline disease assessment showing no evidence of disease progression. For the evaluation of disease progression, an adequate post-baseline assessment is defined as an assessment where there is enough evidence to indicate the subject had progressed or not based on RECIST 1.1 guidelines. In the situation where subjects did not have baseline disease assessment or who did not have adequate post-baseline disease assessment, they will be censored at the date of first dose of study treatment.	Primary Analysis: For each disease cohort, the following analysis methods will be used to perform the analysis based on Efficacy Evaluable population. Kaplan-Meier curve will be provided. The 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median PFS (mPFS) to test the hypotheses. The null hypothesis will be rejected if the confidence interval of the observed mPFS is above the mPFS in the null hypothesis. Kaplan-Meier point estimate and its 2-sided 90% confidence interval will also calculated for PFS rate at selected landmark points. Sensitivity Analyses: • All Treated Population. Same analysis methods . • Subjects who received subsequent anti-cancer treatment will be censored at the last adequate post-baseline disease assessment showing no evidence of PD prior to initiation of subsequent anti-cancer treatment: Efficacy Evaluable Population. Same analysis methods.
Primary Endpoint (UC Cohorts 5 and 6)		
ORR	Proportion of subjects achieving complete response (CR) or partial response (PR) with confirmation based on the best overall response (BOR) per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease	Primary Analysis: For each disease cohort, ORR will be estimated using the Efficacy Evaluable Population according to the crude proportion of subjects meeting the criteria.

Endpoint	Definition	Analysis Methods
	or initiation of subsequent anti-cancer treatment, whichever occurs first. Confirmation of CR or PR requires two consecutive assessments that are at least 28 days apart.	Two-sided 90% confidence interval (CI) for ORR will be calculated using the exact binomial distribution (Clopper-Pearson) to test the null hypothesis. The null hypothesis will be rejected if the confidence interval of the observed ORR is above the ORR in the null hypothesis. Sensitivity Analyses: • All Treated population. Same analysis method. • ORR without confirmation: Efficacy Evaluable Population. Same analysis method. • ORR without confirmation: All Treated Population. Same analysis method. Subgroup Analysis: Forest plots of ORR and its two-sided 90% CIs will be provided for each subgroup to show the trend.
Secondary Endpoints		
ORR (UC Cohort 2)	Same as above	Same as the above primary analysis. No sensitivity analysis will be performed.
PFS (UC Cohorts 5 and 6)	Same as above	Same as the above primary analysis. No sensitivity analysis will be performed.
DOR	Defined for confirmed responders (PR or better) as time from the date of initial response (PR or better) to the date of first documentation of PD or death, whichever occurs first, regardless of use of subsequent anti-cancer treatment. Confirmed responders without documentation of PD or death or with unknown status at the data extraction will be censored at the last adequate post-baseline disease assessment showing no evidence of PD.	If there are enough confirmed responders in the Efficacy Evaluable population, Kaplan-Meier curves will be provided and 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median DOR (mDOR) and Kaplan-Meier point estimates at selected landmark time points. Otherwise, only descriptive statistics will be provided.
DCR	Proportion of subjects achieving CR , PR, or SD of length ≥ 6 weeks (SD only) based on the best overall	Primary Analysis: For each disease cohort, DCR will be estimated using the Efficacy Evaluable

Endpoint	Definition	Analysis Methods
	response (BOR) per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease or initiation of subsequent anti-cancer treatment, whichever occurs first. Confirmation of CR or PR is not required	Population according to the crude proportion of subjects meeting the criteria. Two-sided 90% confidence interval (CI) for DCR will be calculated using the exact binomial distribution (Clopper-Pearson). Sensitivity Analyses: • DCR based on confirmed CR or PR: Efficacy Evaluable Population. Same analysis method. • DCR based on confirmed CR or PR: All Treated Population. Same analysis method.
OS	Time from the date of first dose of study treatment to the date of death from any cause. Subjects who were not known to have died at the data extraction will be censored at date last known alive.	Primary analysis: For each disease cohort, the following analysis methods will be used to perform the analysis based on Efficacy Evaluable population. Kaplan-Meier curve will be provided. The 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median OS (mOS). Kaplan-Meier point estimate and its 90% confidence interval will be calculated for OS rate at selected landmark points. Sensitivity Analysis: All Treated Population. Same analysis methods.

5. SAFETY ASSESSMENTS

Safety data will be summarized using All Treated Population by ibrutinib dose level (RP2D versus other dose level) for each disease cohort separately. Adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the investigator according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

In general, the treatment-emergent (TE) period is defined as the period from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent anti-cancer treatment, whichever comes first.

Treatment-emergent adverse events are those events that:

- Are not present prior to the TE period and occur during the TE period,
- The onset dates are missing and resolution dates are during the TE period,
- Are considered related (at least possibly related) to the study treatment by the investigator regardless of the start dates of the events, or
- Are present prior to the TE period but worsen in severity during the TE period or are subsequently considered related to study drug by the investigator.

Dose limiting toxicities (DLTs) as determined by the investigator and identified by the check box on the Adverse Event page will be summarized for each cohort and dose level TEAE will be presented by relationship to individual study drugs (Cohorts 2 and 6) and also separately for those considered related to both study drugs.

Events of special interest as listed below will be summarized:

- Protocol-defined events of clinical interest including hemorrhagic events and major hemorrhage.
- Other safety observations including tumor lysis syndrome (TLS), neutropenic AEs, infections, atrial fibrillation, cardiac arrhythmias (including ventricular tachyarrhythmia), cardiac failure, other malignancies (including non-melanoma skin cancer, melanoma skin cancer, non-skin cancer), hepatic disorders, interstitial lung disease (ILD), hypertension, ischemic stroke, diarrhea, and sepsis.

All laboratory values will be converted to and reported as international standard (SI) units. In general, only data from the central laboratory will be summarized and analyzed. Laboratory parameters will be graded using the NCI CTCAE, Version 4.03. Unless otherwise specified, only

baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis.

Table 4: Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
Adverse Events	Treatment emergent DLTs, TEAEs, SAEs, Grade 3 or higher TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose delay, TEAEs leading to dose modification, TEAEs leading to death, protocol- defined events of special interest and other safety observations	Descriptive summary statistics and/or listings
Laboratory Parameters	Worst post-baseline toxicity grade for CTCAE gradable hematology and chemistry. Abnormalities in creatinine clearance, uric acid, and liver function.	Descriptive summary statistics and/or listings
Vital Signs and other Observations Related to Safety	Systolic blood pressure (SBP), diastolic blood pressure (DBP), abnormal physical examination findings	Descriptive summary statistics and/or listings

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

5.1. Data Summaries for COVID-19

TEAEs and deaths related to a COVID-19 infection will be summarized and included in the corresponding tables. COVID-19 laboratory tests will be summarized.

6. CHANGES IN PROTOCOL-PLANNED ANALYSIS

No changes have been made in protocol-planned analyses.

7. REFERENCES

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1128 SAP2

Interim Agreement Report 2021-07-07

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1128 SAP2

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Statistical Analysis Plan 1

A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal and Genitourinary Tumors

PCYC-1128-CA

November 12, 2019

Version 1.0

STATISTICAL ANALYSIS PLAN (SAP) APPROVAL

Protocol Number:	PCYC-1128-CA
Protocol Title:	A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal And Genitourinary Tumors
SAP Version:	1.0
Author:	[redacted]
Date:	12 NOV 2019

By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

[redacted] Biostatistics — 11/12/2019 — Date (ddMMMyyyy)

[redacted] Clinical Science — 11/13/2019 — Date (ddMMMyyyy)

[redacted] Regulatory Affairs — 11/13/2019 — Date (ddMMMyyyy)

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[redacted] Biostatistics — 11/13/2019 — Date (ddMMMyyyy)

[redacted] Imbruvica Clinical Science — 11/19/2019 — Date (ddMMMyyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ATC	anatomical therapeutic chemical
CEA	carcinoembryonic antigen
CR	complete response
CRC	colorectal adenocarcinoma
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLRC	dose level review committee
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
RCC	renal cell carcinoma
RP2D	recommended Phase 2 dose
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the protocol Amendment 2.1 and is to define key elements including variable definitions, and statistical methods for analysis of data in evaluation of efficacy and safety of the study PCYC-1128-CA. Analyses of biomarker and pharmacokinetics are not in scope of this document. Throughout this SAP, "study treatment" and "study drug" are used interchangeably, both refer to any of the study drugs including ibrutinib, and/or backbone/standard of care drugs.

Analysis methods specified in this document take precedence over those described in protocol should there be any difference. Any changes from the protocol will be documented in Section 6, Changes in Protocol Planned Analysis.

There will be two CSRs for this study. CSR #1 is for RCC Cohort 1, GC Cohort 3, and CRC Cohort 4 and CSR #2 is for all UC cohorts (Cohorts 2, 5, and 6). Database extraction will take place in the first quarter of 2020 to prepare for CSR #1. This SAP (referred to as SAP1) is to cover the analysis plan for CSR #1. A second SAP (referred to as SAP2) will be written to cover the analysis plan for CSR #2 in the future.

1.1. Study Design

This is an open-label, Phase 1b/2 multi-center study to assess the safety and efficacy of ibrutinib monotherapy (Cohort 5) in subjects with previously-treated urothelial carcinoma (UC) and ibrutinib combination therapy (Cohorts 1-4, 6) in subjects with previously treated renal cell carcinoma (RCC), UC, gastric carcinoma (GC), and colorectal carcinoma (CRC) as listed below. Each cohort in this study will assess a different malignancy and/or anticancer agent in combination with ibrutinib or single-agent ibrutinib and follow an independent and parallel design:

- Metastatic RCC (Cohort 1)
- Advanced (locally recurrent and/or metastatic) UC (Cohorts 2, 5, 6)
- Advanced (locally recurrent and/or metastatic) GC (Cohort 3)
- Metastatic CRC (Cohort 4)

This Phase 1b/2 study is divided into 2 parts. An initial Phase 1b portion will evaluate the safety and tolerability of single-agent ibrutinib and ibrutinib in combination with each anticancer agent to assess any dose limiting toxicity in order to determine the recommended Phase 2 dose (RP2D) for each cohort.

The Phase 2 portion will assess primary endpoints of PFS, progression-free survival, (with an incorporated interim analysis) for RCC and UC cohort 2, and overall response rate (ORR) using a Simon's minimax 2-stage design for GC, CRC, and UC Cohorts 5 and 6.

Phase 1b

The Phase 1b portion of this study is performed independently in six separate cohorts defined by the clinical indication; RCC, UC, GC, and CRC.

For cohorts 1-4, safety and dose-limiting toxicity (DLT) assessment will be evaluated in 3-9 subjects at each dose level in a 3+3+3 design. At each dose level, DLT assessment will be performed in the first 3 subjects. If 1 of 3 subjects experiences a DLT during the first treatment cycle, the same dose level will be expanded to 6 subjects, and if 2 of the 6 experience a DLT, the same dose level will be expanded to 9 subjects. At the 560 mg/day dose level (DL 1), if 0 out of 3, 1 out of 6 or 2 out of 9 subjects (≤22%) experience a DLT during the first treatment cycle, dose escalation to 840 mg/day (DL 2) will occur. At DL 1 (560 mg/day), if ≥33% of subjects experience a DLT (eg, >2 out of 6 or >2 out of 9 subjects), the dose will be de-escalated to 420 mg/day (dose level minus one; DL -1). At the 840 mg/day dose level (DL 2) cohort, subjects will be enrolled in a similar fashion.

For UC cohort 5, the single-agent dose of 840 mg will be confirmed and documented in the first 6 patients; safety data will be described.

For UC cohort 6, a 6+3 dose de-escalation design will be implemented. For the Phase 1b portion of cohort 6, if 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6 subjects experience a DLT, dose de-escalation will occur and additional 6 evaluable subjects will be enrolled. If incidence of DLTs during the DLT observation period is <33.3% (ie, ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2 and will be defined as the RP2D.

The RP2D will be determined when 6–9 subjects at the dose level complete the DLT observation period based on the totality of the data including dose reductions (of both ibrutinib and the combination therapy), treatment-limiting toxicities (outside of DLTs), the available pharmacokinetic data and the toxicity profile obtained during Phase 1b. In order to determine the RP2D dose level, a minimum of 6 DLT-evaluable subjects will be required at the RP2D dose level who are defined to have completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent, after the initiation of therapy at the start of Cycle 1.

For UC cohorts 5 and 6, a DLT-evaluable subject will have ≥ 90% compliance with ibrutinib during Cycle 1 (the first 21 days). At each dose level, the decision of de-escalation will be made for at least 6 DLT-evaluable subjects. However, if at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped.

For combination therapy of ibrutinib and other anticancer agent specified below, the starting dose of ibrutinib will be 560 mg daily in the following 5 cohorts:

RCC cohort 1: ibrutinib + everolimus

UC cohort 2: ibrutinib + paclitaxel

GC cohort 3: ibrutinib + docetaxel

CRC cohort 4: ibrutinib + cetuximab

UC cohort 6: ibrutinib + pembrolizumab

For single-agent ibrutinib, the starting dose will be 840 mg.

UC cohort 5: single-agent ibrutinib

A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort to determine the RP2D, prior to continuing with enrollment into the Phase 2 portion (enrollment may not be held for UC cohort 5 as safety data is available for more than 40 subjects for ibrutinib 840 mg in combination with paclitaxel data). The DLRC will review the safety data in the first 6 evaluable subjects enrolled in cohort 5 to confirm 840 as the single-agent dose. Members of this committee will include the Medical Monitor or designee, a Drug Safety representative, a Biostatistician, and at least 2 participating investigators/designees.

The DLT observation period will encompass 21 days after the initiation of combination therapy (or single agent ibrutinib for Cohort 5) at the start of Cycle 1. A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic adverse event (AE) occurring during the DLT observation period and considered to be at least possibly related to the study treatment (ibrutinib or combination). Details of DLTs are documented in the protocol Section 3.

If a subject experience a DLT during the DLT observation period, the subject will discontinue treatment. Dose reductions will not be permitted during the DLT observation period. However, any other subject(s) tolerating the dose level through the DLT observation period will continue to receive the same dose of study drugs even if a dose escalation or de-escalation occurs for subsequent study subjects.

Any Phase 1b subjects who discontinue one or more study drugs, or require dose reduction within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced, unless the discontinuation is in association with a DLT. Subjects who miss one or more scheduled doses (more than 2 doses for UC cohorts 5 and 6) of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will continue. However, such a subject will not be evaluable for DLT assessment and will be replaced for DLT assessment purposes.

After Cycle 1, all subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. Tumor assessment by CT/MRI will occur every 6 weeks and will be evaluated according to RECIST 1.1 guidelines. After the RP2D has been defined for each cohort, enrollment in Phase 2 will commence in that cohort.

Dosing regimen in Phase 1b for each cohort is described in Table 1 below:

Table 1: Dosing Regimen in Phase 1b

Cohort	DL-1	DL 1	DL2
RCC (Cohort 1)	Ibrutinib: 420 mg PO qd Everolimus: 10 mg PO qd	Ibrutinib: 560 mg PO qd Everolimus: 10 mg PO qd	Ibrutinib: 840 mg PO qd Everolimus: 10 mg PO qd
UC (Cohort 2)	Ibrutinib: 420 mg PO qd Paclitaxel: 80 mg/m^2 IV qweek	Ibrutinib: 560 mg PO qd Paclitaxel: 80 mg/m^2 IV qweek	Ibrutinib: 840 mg PO qd Paclitaxel: 80 mg/m^2 IV qweek
GC (Cohort 3)	Ibrutinib: 420 mg PO qd Docetaxel: 60-75 mg/m^2 IV q3weeks	Ibrutinib: 560 mg PO qd Docetaxel: 60-75 mg/m^2 IV q3weeks	Ibrutinib: 840 mg PO qd Docetaxel: 60-75 mg/m^2 IV q3weeks
CRC (Cohort 4)	Ibrutinib: 420 mg PO qd Cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 IV qweek	Ibrutinib: 560 mg PO qd Cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 IV qweek	Ibrutinib: 840 mg PO qd Cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 IV qweek
UC (Cohort 5)	Ibrutinib 560 mg PO qd	Ibrutinib 840 mg PO qd	NA
UC (Cohort 6)	Ibrutinib: 420 mg PO qd Pembrolizumab: 200 mg IV q3weeks	Ibrutinib: 560 mg PO qd Pembrolizumab: 200 mg IV q3weeks	NA

PO = orally, qd = daily, qweek = weekly, q3weeks = every 3 weeks
Study treatment will be given in 21-day cycles for all cohorts.

Phase 2

For each cohort in the study, a separate analysis will be performed to evaluate the response and safety profile. Tumor assessment by CT/MRI will occur every 6 weeks and will be evaluated according to RECIST 1.1 guidelines. Subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. Subjects treated at RP2D in Phase 1b will be included in Phase 2 analyses.

In all cohorts, subjects who are dosed at the RP2D level and withdraw prior to the completion of at least 2 cycles of study treatment, for reasons other than unacceptable toxicity or disease progression, may be replaced after consultation with the Sponsor.

For GC (Cohort 3), CRC (Cohort 4), and UC Cohorts 5 and 6, if a subject in Stage-1 discontinues prior to the first tumor response assessment for reasons other than disease progression, the subject may be replaced. Enrollment may continue into stage-2, while the response evaluation and analysis from the Stage-1 are completed. If the number of responders observed among the evaluable subjects in Stage-1 is less than the number of responders required to proceed per the Simon's 2-stage design, the relevant cohort may be terminated for futility.

1.2. Endpoints

The rest of this SAP1 document only describes endpoints and analysis relevant to CSR #1.

1.2.1. Primary Endpoint

Phase 1b

- To determine the RP2D of ibrutinib in combination with everolimus in RCC, docetaxel in GC and cetuximab in CRC and assess DLTs during the 21-day DLT assessment period.

Phase 2

- Progression-free survival (PFS) in accordance with RECIST 1.1 criteria in RCC in Cohort 1
- Overall response rate (ORR) in GC in Cohort 3 and CRC in Cohort 4

1.2.2. Secondary Endpoints

Phase 1b

- Secondary objectives are to assess ORR and disease control rate (DCR).

Phase 2

- Disease control rate (DCR) in all cohorts
- PFS in GC Cohort 3 and CRC Cohort 4
- ORR in RCC Cohort 1
- Overall survival (OS) in all cohorts
- Duration of response (DOR) in all cohorts

1.2.3. Safety Assessments

Phase 1b

- To assess the safety and tolerability of ibrutinib in each cohort

Phase 2

- Safety and tolerability of ibrutinib combination therapy in each cohort

1.2.4. Exploratory Endpoints (Phase 2)

- [redacted]

1.3. Statistical Hypotheses

For each cohort, the design will provide approximately 80% power to perform one-sided hypothesis testing at α level of 0.05.

Cohort	Hypothesis Testing
RCC Cohort 1	H_0: $m \leq 4.9$ months versus H_1: $m \geq 8.6$ months, where m is the median PFS.
GC Cohort 3	H_0: $\pi \leq 7\%$ versus H_1: $\pi \geq 20\%$, where π is the overall response rate.
CRC Cohort 4	H_0: $\pi \leq 10\%$ versus H_1: $\pi \geq 25\%$, where π is the overall response rate.

H_0 is the null hypothesis. H_1 is the alternative hypothesis.

1.4. Sample Size Determination

The number of subjects required to be treated with ibrutinib at the RP2D level for the efficacy evaluation is determined for each disease cohort using the following methods.

RCC Cohort 1

The primary endpoint is PFS. A sample size of approximately 55 efficacy evaluable subjects provides 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS ≤4.9 months versus the alternative hypothesis median PFS ≥8.6 months. The median PFS for everolimus is assumed to be 4.9 months under the null hypothesis. The study is designed to detect a 75% increase in median PFS to 8.6 months for ibrutinib in combination with everolimus. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve a minimum of 80% power is determined by a simulation method with an enrollment rate of 5 subjects per month and with the data cut time for analysis to be at 6 months following the last subject enrollment.

GC Cohort 3

The primary endpoint is ORR. In this Simon's 2-stage design a total of 39 subjects are to be enrolled in two stages. In Stage-1, 21 subjects will be enrolled and if at least 2 subjects are responders; an additional 18 subjects will be enrolled in stage2. At the end of the study if there are 6 or more responders, then the null hypothesis is rejected, and the study treatment would be considered acceptable for further clinical development.

This Simon's 2-stage minimax design provides at least 80% power to test the historical ORR rate of 7% (null hypothesis) against the target ORR of 20% (alternative hypothesis) at a 1-sided significance level of 0.05.

CRC Cohort 4

The primary endpoint is ORR. In this Simon's 2-stage design a total of 40 subjects are to be enrolled in two stages. In Stage-1, 22 subjects will be enrolled and if at least 3 subjects are responders; an additional 18 subjects will be enrolled in stage-2. At the end of the study if there are 8 or more responders, then the null hypothesis is rejected, and the study treatment would be considered acceptable for further clinical development.

This Simon's 2-stage design provides at least 80% power to test the historical ORR rate of 10% (null hypothesis) against the target ORR of 25% (alternative hypothesis) at a 1-sided significance level of 0.05.

Table 2 below provides a summary for number of subjects needed in Stage 1 and Stage 2 of Simon's 2-stage design for cohorts 3 and 4 in order to declare success.

Table 2: Number of Subjects and Number of Responders for Simon's 2-stage Minimax Design

Cohort (Total Number of Subjects)	Number of Subjects for Stage 1	Number of Responders in Stage 1 Needed to proceed to Stage 2	Number of Subjects for Stage 2	Number of Responders Need to Reject the Null Hypothesis for the Study
GC Cohort 3 (N=39)	21	≥ 2 (≤ 1)	18	≥ 6
CRC Cohort 4 (N=40)	22	≥ 3 (≤ 2)	18	≥ 8

1.5. Planned Analysis

1.5.1. Phase 1b analysis

Analysis for Phase 1b will be conducted separately for each disease cohort and dose level when appropriate.

1.5.2. Interim Analysis (IA)

An interim analysis will be conducted for each cohort independently for the Efficacy Evaluable Population. Cohorts 3 (GC) and 4 (CRC) were based on Simon's 2-stage design and the interim

analysis stopping rule was determined by the design. For Cohort 1 (RCC), interim analysis timing is when approximately 25 efficacy evaluable subjects dosed at the RP2D level have completed 6 months of follow-up. Details are provided below. Enrollment may continue while the interim analysis is being performed for each cohort. The analysis will be conducted on subjects who received RP2D from Phase 1b and Phase 2.

Go/No Go decisions at the time of the interim analyses will include all available clinical and safety data for that cohort and are not based solely on the efficacy data for the endpoint involved in the interim analysis. No multiplicity adjustment will be made for Cohort 1 final efficacy analysis.

RCC Cohort 1

PFS is the primary efficacy endpoint for this cohort. A single interim analysis for futility will take place after approximately 25 efficacy evaluable subjects dosed at the RP2D level have completed 6 months of follow-up. The proportion of subjects that are PFS event-free at 6 months will be assessed along with other safety and efficacy data in making the determination if the study should continue. Point estimator and 2-sided 90% Brookmeyer-Crowley confidence interval with log-log-transformed Greenwood variance estimate of the median PFS (mPFS) will be calculated to assess efficacy.

GC Cohort 3 and CRC Cohort 4

For those two cohorts, ORR is the primary endpoint and Simon's 2-stage minimax design is implemented to evaluate ORR following the Stage-1 boundaries in Table 2.

At the interim analysis of the Stage-1, the proportion of responding subjects (best response of CR or PR) will be calculated, along with other safety and efficacy data when making the determination if the study should continue into the stage-2. Confirmation of response is not required for the interim analysis.

1.5.3. Final Analysis

The final analysis will be conducted after all efficacy evaluable subjects have completed a minimum period of follow-up for the primary endpoint or other key endpoint(s).

There will be two CSRs for this study. CSR #1 is for RCC Cohort 1, GC Cohort 3, and CRC Cohort 4 and is covered in SAP1. When all subjects in these three cohorts have exited the study, an addendum will be written to summarize disposition and selected safety data.

RCC Cohort 1

Primary endpoint for RCC Cohort 1 is PFS. Final analysis will be performed 6 months after last enrolled subject (LPI) completes the treatment and assessment.

GC Cohort 3 and CRC Cohort 4

Primary endpoint for those two cohorts is ORR. Confirmation of response is required for the final analysis per RECIST 1.1 since this is an open label single arm study. That is, CR or PR may be claimed only if the criteria for each are met at a subsequent visit (generally 4 weeks or later). See Table 3 in RECIST 1.1 [2] for the scenarios of the best overall response when confirmation is required.

1.5.4. Blinding and Randomization Methods

Not Applicable. This is an open-label non-randomized study.

2. GENERAL ANALYSIS CONSIDERATION

Phase 1b

Limited tables and listings will be included. They are baseline demographic, baseline characteristics, disease characteristics, treatment and study disposition, DLTs, ORR, DCR, overview of treatment emergent adverse events (TEAEs), TEAEs by Systems Organ Class/Preferred Term/maximum severity, serious TEAEs, TEAEs leading to death, TEAEs leading to ibrutinib discontinuation. No subgroup will be summarized for this phase. Data will be summarized separately for each cohort by dose.

Phase 2

Data summary and data analysis will be conducted for each disease cohort separately. Data will not be pooled across disease cohorts or tested between disease cohorts.

Baseline, demographics, disposition, and safety data will be summarized by dose level (RP2D). Efficacy analysis will only be conducted for subjects treated at R2PD. Subjects who were treated with ibrutinib at the R2PD level in Phase 1b or Phase 2 will be combined in the summary.

Subgroup analyses are mainly to evaluate for trends and assess internal consistency of any treatment benefit. Analysis will be carried out for the CRC and GC cohorts only. The subgroups for these cohorts are of clinical interest/relevance. Statistical hypothesis testing will not be performed for the subgroup analyses.

General Definitions:

For disease cohorts with a combination treatment, date of first dose of study treatment is defined as the date the subject received the first dose of ibrutinib or the companion drug (whichever occurs first) and date of last dose of study treatment is defined as the date the subject receive the last dose of ibrutinib or the companion drug (whichever occurs later).

Baseline value is defined as the last non-missing valid value collected prior to the first administration of study treatment. For subjects who have been enrolled but not treated, enrollment date will be used as the reference date for baseline if needed.

2.1. Analysis Sets

DLT Evaluable Population: Defined as subjects from Phase 1b who completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent after the initiation of study treatment at the start of Cycle 1, or those who discontinued from study treatment due to a DLT event prior to completion of DLT observation period. The DLT Evaluable Population will be used for DLT assessments. Per protocol, subjects who miss one or more scheduled doses of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will

continue. However, such a subject will not be evaluable for DLT assessment, and will be replaced for DLT assessment purposes.

All Enrolled Population: Defined as all eligible subjects enrolled in the study.

All Treated Population: Defined as all subjects who received at least 1 dose of study treatment (ibrutinib or the companion drug for the combination therapy). This population is the same as the Safety Population defined in the protocol. For the purpose of analysis and CSR, All Treated Population will be used as the data set to summarize all the data unless otherwise indicated. Sensitivity analysis of efficacy endpoints will be performed based on this population.

Efficacy Evaluable Population: This population will be used to perform the primary analysis for the efficacy endpoint(s) and is defined as eligible subjects who received at least one dose of ibrutinib (at RP2D) in combination with at least one dose of the relevant companion drug and fulfil the following criteria:

RCC Cohort 1 (PFS as the primary endpoint)

1) Had at least one adequate post-baseline overall disease assessment per RECIST 1.1 guidelines or died prior to the first adequate post-baseline overall disease assessment.

GC Cohort 3 and CRC Cohort 4 (ORR as the primary endpoint)

1) Had measurable disease (i.e. at least one target lesion as defined in the protocol) per RECIST 1.1 guidelines at baseline.

2) Had at least one adequate post-baseline overall disease assessment per RECIST 1.1 guidelines.

2.2. Definition of Subgroups

Subgroup analyses will be performed for the selected variables in an exploratory fashion. Further clinically relevant and biomarker subgroups will be assessed at the time of the final CSR if appropriate. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data. Otherwise subgroup analysis will not be carried out if the distribution for the subgroup variable does not warrant the analysis.

Subgroup analysis is relevant only for the primary endpoints of GC and CRC cohorts.

Table 3.1: Baseline Subgroup Definition

Cohort	Subgroup	Definition of Subgroup	Analysis Type
CRC and GC	Renal function (creatinine clearance)	< 30, 30 - < 60, ≥ 60 mL/min	E
	Hepatic function (NCI ODWG definition)	normal, mild, moderate, severe (or normal vs. non-normal as appropriate)	E
	ECOG	0, ≥ 1	E
	Liver metastasis	Present, absent	E
CRC only	Active and indolent progressors	Active, indolent progressors[a]	E
	Number of prior therapies in metastatic setting	≥ 3, < 3	E
GC only	Number of prior therapies in metastatic setting	1, ≥ 2	E

Analysis type: E = Efficacy – Primary endpoint only (PFS or ORR).

[a] Active progressors defined as ≤ 180 days from the last dose of last therapy to first dose of ibrutinib. Indolent progressors defined as > 180 days from the last dose of last therapy to first dose of ibrutinib.

Table 3.2: Post-Baseline Subgroup Definition

Subgroup	Definition of Subgroup	Analysis Type
Worst toxicity grade of treatment emergent rash for CRC only	0, 1-2, and > 2	Efficacy – ORR

Rash for CRC cohort is defined by the SMQ terms.

3. SUBJECT INFORMATION

Subject information will be summarized descriptively by ibrutinib dose level (RP2D versus other dose level) for each disease cohort individually. Subjects who were treated with ibrutinib at the R2PD level in Phase 1b or Phase 2 will be combined in the summary.

3.1. Subject Disposition

Subject enrollment will be summarized by country and investigator/site. Subject disposition for each study drug and for study participation will be tabulated. Overall treatment duration and time on study will be summarized.

The disposition tables will include the following summaries:

- Analysis populations (all enrolled subjects)

- Enrollment by country and investigator/site (all enrolled subjects)
- Study treatment disposition, study treatment duration and discontinuation of study treatment (All Treated Population)
- Study status and study exit for all enrolled subjects.

Time on study is defined in the same way as overall survival with reversed censoring, i.e., subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

3.2. Demographics, Baseline Characteristics, and Baseline Disease Characteristics

Subject demographics and baseline characteristics will be summarized with descriptive statistics for the all treated population by cohort.

3.3. Prior and Concomitant Medications

Medications will be coded to a generic name and an Anatomical Therapeutic Chemical (ATC) class according to World Health Organization drug dictionary.

Prior medications are defined as medications that started prior to the first dose of study treatment. Concomitant medications are defined as medications that were taken on treatment (i.e. from the date of first dose of study treatment through the date of last dose of study treatment).

Concomitant medications will be summarized by ATC class and preferred term (PT) based on All Treated Population for each disease cohort. Each subject will be counted once only for overall, each PT, and each ATC class. The following concomitant medications will be summarized separately:

- CYP3A inhibitors and inducers – This list requires a medical review, with finalization at the time of analysis
- Anticoagulants and antiplatelet agents will need medical review as above.

3.4. Extent of Exposure to Study Treatment

For each disease cohort, exposure to study treatment will be summarized for each study drug for the All Treated Population. Descriptive statistics will be provided, by study drug, for the followings: treatment duration (month), total number of doses received, total number of cycles received (for chemotherapy), total cumulative dose administered, dose intensity and relative dose intensity (%), and number (%) of subjects with dose reduction due to adverse events (AEs), dose delay due to AEs and dose reduction or delay due to AEs.

3.5. Prior Anti-cancer Treatments and Subsequent Anti-cancer Treatment

Anti-cancer treatment includes drug therapies, radiation, and surgeries and procedures performed with therapeutic intent. The ATC level of anti-cancer drug therapies will be specified in the mock-up table footnote. Prior anti-cancer treatments are treatments received prior to study treatment. Subsequent anti-cancer treatment are treatments received after date of last dose of study treatment. Prior and subsequent anti-cancer treatment will be summarized separately using All Treated population for each disease cohort.

4. ANALYSIS FOR ENDPOINTS

For Phase 1b, data will be summarized by dose level for each cohort separately. As described in Sections 1.5 and 2, limited tables and listings will be included. Descriptive summaries will be provided and confidence intervals described in Table 4 for ORR, DCR can be applied as data warrant. No subgroup will be summarized for this phase.

For Phase 2, efficacy and safety data will be summarized by RP2D dose level of ibrutinib (same RP2D in both phases will be pooled together) for each disease cohort separately. Hereafter this will be referred to as "Phase 1b/2 RP2D" in the tables.

Primary analysis of each efficacy endpoint will be performed using the Efficacy Evaluable Population at the time of final analysis, unless otherwise indicated. Sensitivity analyses will be performed for some efficacy endpoints using the All Treated Population. Safety data will be summarized using the All Treated Population.

Efficacy analyses will be based on the overall disease assessments determined by the investigator per RECIST 1.1 guidelines. Efficacy endpoint definitions and analysis methods for Phase 2 are described in Table 4.

Table 4: Summary of Efficacy Analyses

Endpoint	Definition	Analysis Methods
Primary Endpoint (RCC)		

Endpoint	Definition	Analysis Methods
PFS	Time from the date of first dose of study treatment to the date of first documentation of progressive disease (PD) or date of death from any cause, whichever occurs first, regardless of the use of subsequent anti-cancer treatment. Subjects who were not known to have disease progression or death at the data extraction will be censored at date of last adequate post-baseline disease assessment showing no evidence of disease progression. For the evaluation of disease progression, an adequate post-baseline assessment is defined as an assessment where there is enough evidence to indicate the subject had progressed or not based on RECIST 1.1 guidelines. In the situation where subjects did not have baseline disease assessment or who did not have adequate post-baseline disease assessment, they will be censored at the date of first dose of study treatment.	Primary Analysis: For each disease cohort, the following analysis methods will be used to perform the analysis based on Efficacy Evaluable population. Kaplan-Meier curve will be provided. The 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median PFS (mPFS) to test the hypotheses. The null hypothesis will be rejected if the confidence interval of the observed mPFS is above the mPFS in the null hypothesis. Kaplan-Meier point estimate and its 2-sided 90% confidence interval will also calculated for PFS rate at selected landmark points. Sensitivity Analyses: • All Treated Population. Same analysis methods . • Subjects who received subsequent anti-cancer treatment will be censored at the last adequate post-baseline disease assessment showing no evidence of PD prior to initiation of subsequent anti-cancer treatment: Efficacy Evaluable Population. Same analysis methods.
Primary Endpoint (GC and CRC)		
ORR	Proportion of subjects achieving complete response (CR) or partial response (PR) with confirmation based on the best overall response (BOR) per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease or initiation of subsequent anti-cancer treatment, whichever occurs first. Confirmation of CR or PR requires	Primary Analysis: For each disease cohort, ORR will be estimated using the Efficacy Evaluable Population according to the crude proportion of subjects meeting the criteria. Two-sided 90% confidence interval (CI) for ORR will be calculated using the exact binomial distribution (Clopper-Pearson) to test the null hypothesis. The null hypothesis will be rejected if the confidence interval of

Endpoint	Definition	Analysis Methods
	two consecutive assessments that are at least 28 days apart.	the observed ORR is above the ORR in the null hypothesis. Sensitivity Analyses: • All Treated population. Same analysis method. • ORR without confirmation: Efficacy Evaluable Population. Same analysis method. • ORR without confirmation: All Treated Population. Same analysis method. Subgroup analysis: Forest plots of ORR and its two-sided 90% CIs will be provided for each subgroup to show the trend.
Secondary Endpoints		
ORR (RCC)	Same as above	Same as the above primary analysis. No sensitivity analysis will be performed.
PFS (GC and CRC)	Same as above	Same as the above primary analysis. No sensitivity analysis will be performed.
DOR	Defined for confirmed responders (PR or better) as time from the date of initial response (PR or better) to the date of first documentation of PD or death, whichever occurs first, regardless of use of subsequent anti-cancer treatment. Confirmed responders without documentation of PD or death or with unknown status at the data extraction will be censored at the last adequate post-baseline disease assessment showing no evidence of PD.	If there are enough confirmed responders in the Efficacy Evaluable population, Kaplan-Meier curves will be provided and 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median DOR (mDOR) and Kaplan-Meier point estimates at selected landmark time points. Otherwise, only descriptive statistics will be provided.
DCR	Proportion of subjects achieving CR , PR, or SD of length $\geq$ 6 weeks based on the best overall response (BOR) per RECIST 1.1 guidelines recorded since date of first dose of study treatment until first documentation of progressive disease or initiation of subsequent anti-cancer treatment,	Primary Analysis: For each disease cohort, DCR will be estimated using the Efficacy Evaluable Population according to the crude proportion of subjects meeting the criteria. Two-sided 90% confidence interval (CI) for

Endpoint	Definition	Analysis Methods
	whichever occurs first. Confirmation of CR or PR is not required.	DCR will be calculated using the exact binomial distribution (Clopper-Pearson).
OS	Time from the date of first dose of study treatment to the date of death from any cause. Subjects who were not known to have died at the data extraction will be censored at date last known alive.	Primary analysis: For each disease cohort, the following analysis methods will be used to perform the analysis based on Efficacy Evaluable population. Kaplan-Meier curve will be provided. The 2-sided 90% Brookmeyer-Crowley confidence interval (CI) based on the log-log-transformed Greenwood variance estimate will be calculated for median OS (mOS). Kaplan-Meier point estimate and its 90% confidence interval will be calculated for OS rate at selected landmark points. Sensitivity analysis: All Treated Population. Same analysis methods.

5. SAFETY ASSESSMENTS

Safety data will be summarized using All Treated Population by ibrutinib dose level (RP2D versus other dose level) for each disease cohort separately. Adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the investigator according the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

In general, the treatment-emergent (TE) period is defined as the period from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent anti-cancer treatment, whichever comes first.

Treatment-emergent adverse events are those events that:

- Are not present prior to the TE period and occur during the TE period,
- The onset dates are missing and resolution dates are during the TE period,
- Are considered related to the study treatment by the investigator regardless of the start dates of the events, or
- Are present prior to the TE period but worsen in severity during the TE period or are subsequently considered related to study drug by the investigator.

Treatment emergent dose limiting toxicities (DLTs) as determined by the investigator and identified by the check box on the Adverse Event page will be summarized for each cohort.

All laboratory values will be converted to and reported as international standard (SI) units. In general, only data from the central laboratory will be summarized and analyzed. Laboratory parameters will be graded using the NCI CTCAE, Version 4.03. Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis.

Table 5: Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
Adverse Events	Treatment emergent DLTs, TEAEs, SAEs, Grade 3 or higher TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to dose delay, TEAEs leading to dose modification, TEAEs leading to death, protocol- defined events of special interest and other safety observations	Descriptive summary statistics and/or listings
Laboratory Parameters	Worst post-baseline toxicity grade for CTCAE gradable hematology and chemistry. Abnormalities in creatinine clearance, uric acid, and liver function. CEA levels (for CRC Cohort 4 only)	Descriptive summary statistics and/or listings
Vital Signs and other Observations Related to Safety	Systolic blood pressure (SBP), diastolic blood pressure (DBP), abnormal physical examination findings	Descriptive summary statistics and/or listings

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

6. CHANGES IN PROTOCOL PLANNED ANALYSIS

a) "All Treated Population" is the same as the "Safety Population" defined in the protocol Section 10.1.2. However, for analysis purpose and CSR, "All Treated Population" will be used as the data set for efficacy and safety analyses.

b) All Treated Population is used for sensitivity analysis for the primary efficacy endpoints and OS analysis.

c) Other than changes in CEA levels, analysis for other exploratory endpoints are not covered in the scope of the SAP.

d) Subgroup analyses will only be performed for the respective primary endpoints in the GC and CRC cohorts for CSR #1. Analysis for CSR #2 will be discussed in SAP2 to be finalized later.

7. REFERENCES

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