Official Title:	**A Phase 2, Open-Label, 2-Cohort, Multicenter Study of INCB050465, a PI3Kδ Inhibitor, in Relapsed or Refractory Mantle Cell Lymphoma Previously Treated With or Without a BTK Inhibitor (CITADEL-205)**
NCT Number:	NCT03235544
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Statistical Analysis Plan

INCB 50465-205

A Phase 2, Open-Label, 2-Cohort, Multicenter Study of INCB050465, a PI3Kδ Inhibitor, in Relapsed or Refractory Mantle Cell Lymphoma Previously Treated With or Without a BTK Inhibitor (CITADEL-205)

IND Number:	**121,474**
EudraCT Number:	**2017-003148-19**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 7 dated 30 JAN 2020**
CRF Approval Date:	**26 NOV 2018**
SAP Version:	**Amendment 2**
SAP Author:	[redacted], PhD [redacted]
Date of Plan:	**28 JAN 2021**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
BTK	Bruton's tyrosine kinase
CI	confidence interval
[redacted]	[redacted]
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EWB	emotional well-being
[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FWB	functional well-being
[redacted]	[redacted]
IDMC	independent data monitoring committee
IRC	independent review committee
LYMS	lymphoma subscale
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
NCI	National Cancer Institute

Abbreviation	Term
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PJP	*Pneumocystis jirovecii* pneumonia
[redacted]	[redacted]tic
PP	per protocol (population)
PR	partial response
PT	preferred term
PWB	physical well-being
QD	once daily
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
SWB	social/family well-being
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, open-label, 2-cohort study designed to evaluate the efficacy and safety of 2 INCB050465 treatment regimens in relapsed or refractory MCL participants previously treated either with or without a BTK inhibitor.

Section 1 of the Protocol provides a detailed description of the investigational product, target participant population, rationale for doses to be examined, and potential risks and benefits of treatment with INCB050465.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 50465-205 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee, [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 50465-205 Protocol Amendment 7 dated 30 JAN 2020 and CRFs approved 26 NOV 2018. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of INCB050465 in terms of ORR in participants with MCL that is relapsed or refractory after at least 1 but no more than 3 prior systemic treatment regimens.	ORR defined as the percentage of participants with a CR or PR as determined by IRC assessment of response according to CT-based response criteria for lymphomas (Cheson et al 2014).
Secondary	
To assess DOR.	DOR defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among participants who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess CRR.	CRR defined as the percentage of participants with a CR as defined by response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
To assess PFS.	PFS defined as the time from the date of the first dose of study treatment until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
To assess OS.	OS defined as the time from the date of the first dose of study treatment until death from any cause.
To assess the best percentage change in target lesion size.	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of diameters of all target lesion sizes.
To characterize the safety and tolerability of INCB050465.	Safety measured by AEs, 12-lead ECGs, chemistry and hematology laboratory values, vital signs, and physical examinations.
[redacted]	

3. STUDY DESIGN

This is a Phase 2, open-label, 2-cohort study designed to evaluate the efficacy and safety of 2 INCB050465 treatment regimens in relapsed or refractory MCL previously treated either with or without a BTK inhibitor (see Figure 1). Participants will be allocated to Cohort 1 or Cohort 2 as follows:

- Cohort 1: Participants have previously received ibrutinib
- Cohort 2: Participants have not previously received a BTK inhibitor

However, Cohort 1 was closed to further enrollment per Protocol Amendment (Version) 7. Cohort 1 and Cohort 2 will have separate designs, conduct, and analyses. Participants enrolled in Cohort 1 and the first 60 participants in Cohort 2 will be further allocated to 1 of 2 study treatment regimens as follows:

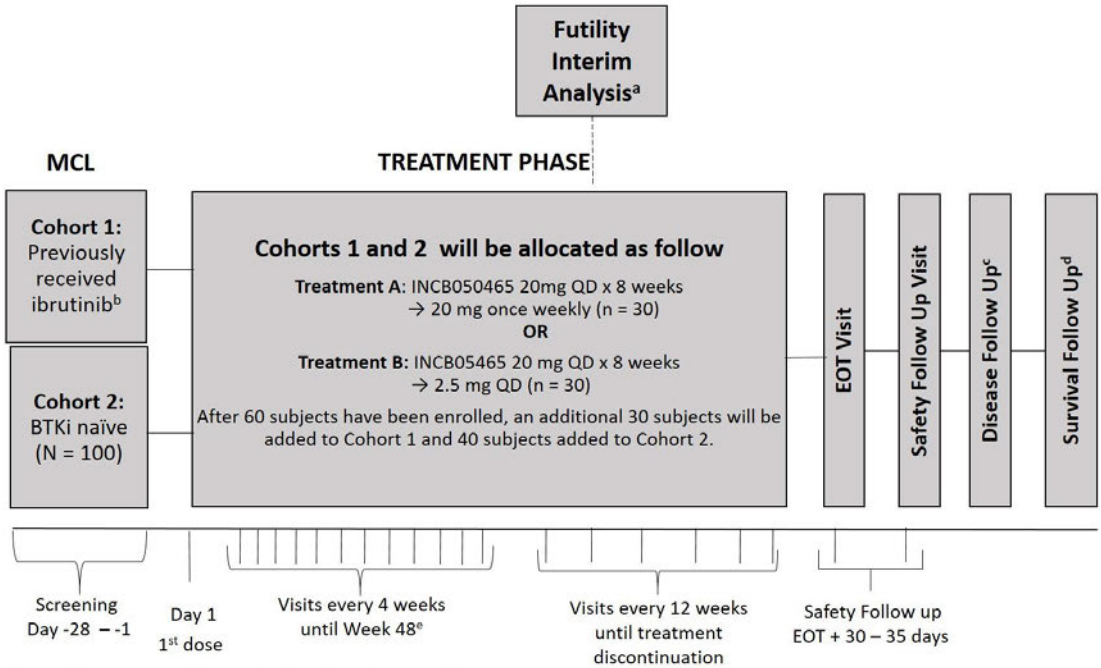
- Treatment A: INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly
- Treatment B: INCB050465 20 mg QD for 8 weeks followed by 2.5 mg QD

An interim futility analysis is planned for each of the cohorts when 30 participants have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Cohort 1 will be terminated for futility if ≤ 3 of the 30 participants responded (ie, CR or PR) based on assessments provided by the IRC. Cohort 2 will be terminated for futility if ≤ 10 of the 30 participants have responded (ie, CR or PR) based on assessments provided by the IRC.

To better understand the safety and efficacy of INCB050465, a total of 70 additional participants (30 participants in Cohort 1 and 40 participants in Cohort 2) will be enrolled into 1 of the 2 treatment regimens being evaluated in this study. The treatment regimen will be selected after enrollment is completed for either Cohort 1 or Cohort 2 (ie, 60 participants enrolled) and after evaluation of emerging safety and efficacy data from this and other monotherapy studies of INCB050465 in non-Hodgkin lymphoma. Once a treatment regimen is selected, the nonselected treatment regimen will be closed to further enrollment. Participants receiving the nonselected treatment regimen may switch to the selected treatment regimen or remain on their current treatment regimen, provided they have not met study-treatment withdrawal criteria and there are no safety concerns for their current treatment regimen. There will be no rebaselining for participants who switch treatment regimens and all participants will continue to follow the same assessment schedule.

Participants will receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal, whichever occurs first. Participants will be evaluated for ORR by an IRC and followed for DOR, PFS, and OS.

Figure 1: Study Design of INCB 50465-205



EOT = end of treatment; MCL = mantle cell lymphoma; QD = once daily
[a] A futility analysis will be performed for each of the cohorts when the first 30 patients in each cohort have been treated and evaluated for response (see Section 9.6). Final analysis will occur when all subjects in the respective Cohort have received at least 1 postbaseline disease assessment, or have progressed, withdrawn from the study, or died.
[b] Cohort 1 will be closed to further enrollment by Protocol Amendment 7 with approximately 50 subjects enrolled.
[c] Subjects who discontinue study treatment for a reason other than disease progression will continue with disease assessments by radiologic imaging per the Schedule of Assessments.
[d] Every 12 weeks by clinic visit, telephone, or e-mail.
[e] Urine pregnancy and dispensing of study treatment will occur every 4 weeks.

3.1. Randomization

Not applicable.

3.2. Control of Type I Error

There will not be any statistical comparison between Cohorts 1 and Cohort 2. Within each of the 2 cohorts, there will not be any statistical comparison between the 2 treatment regimens, and 2-sided 95% CIs will be reported for all analyses when appropriate.

Within each cohort, no adjustment for alpha spending is considered as there are no plans to stop the study early for overwhelming efficacy. An IDMC will be assembled to monitor safety data and study conduct on a regular and ongoing basis during the study. The IDMC will also be charged with evaluating interim futility results. See Section 10 for details regarding interim analyses conducted in this study.

3.3. Sample Size Considerations

Cohort 1 was closed to further enrollment with Protocol Amendment (Version) 7.

The study will enroll up to 100 participants into Cohort 2. If the true ORR is 60%, then there is approximately 90% or 97% probability of observing the lower bound of the 95% CI of ORR ≥ 40% with 60 or 100 participants, respectively.

3.4. Schedule of Assessments

See Protocol Amendment 7 dated 30 JAN 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study drug (INCB050465) is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of INCB050465, unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections. The original reported dates collected on the

eCRF should be used in all relevant listings. The following rules will be used for handling missing or partial dates for analyses requiring dates.

When calculating time since initial diagnosis of cancer, partial diagnosis date will be handled in the calculation as follows:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN will be used.
- Otherwise, the time since diagnosis will not be calculated.

When the date of the last dose is used in deriving variables such as duration of treatment or TEAE flag, missing or partial date of last dose will be handled in the calculation as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

When calculating DOR, PFS, and OS, a partial date of death will be handled in the calculation as follows:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the day after the last known alive date will be used.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the first day of the death month will be used.
- Otherwise, the partial death date will not be handled.

When calculating time to onset or duration of a TEAE, a partial or missing AE onset/end date will be handled in the calculation as follows:

- If only the day is missing, then the first day of the month or Day 1, whichever is later, will be used as the onset date; the earlier date of the last day of the month or the date that the participant discontinued study or died will be used as the end date.
- If both the month and day are missing, then 01 JAN or Day 1, whichever is later, will be used as the onset date; the earlier date of 31 DEC or the date that the participant discontinued study or died will be used as the end date.
- Otherwise, Day 1 will be used as the onset date, and the missing end date will not be handled.

4.2. Variable Definitions

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB050465.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB050465 and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB050465 and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB050465. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 10.

5.2. Treatment Groups

This is a Phase 2, open-label, 2-cohort study. All analyses will be conducted independently for Cohort 1 and Cohort 2, and there will not be multiplicity adjustment between the cohorts. Within each cohort, there will not be any statistical comparison between the treatment groups.

For analysis purposes, the 20 mg once weekly dosing period and the 2.5 mg QD dosing period in Group A and Group B, respectively, are considered maintenance dosing periods. Within each of the 2 cohorts, data will be presented in summary tables by actual received treatment regimen and combined, with an exception for participants who cross over to the selected treatment regimen after the start of the maintenance dosing period.

For participants who cross over from the initially assigned treatment regimen to the selected treatment regimen, if the crossover happens on/prior to the start of the maintenance dosing period then the participant will be summarized, according to the actual received treatment, in the selected treatment regimen; otherwise, the participant will be summarized in:

- A separate treatment regimen (ie, Crossover) for the safety summaries during the maintenance dosing period (eg. summaries of TEAEs and exposure).
- The initially assigned treatment regimen for all other summaries.

Per Protocol Amendment (Version) 7, Cohort 1 was closed to further enrollment. If the number of participants who have enrolled in Cohort 1 is relatively few, summary tables will be replaced with listings.

5.3. Analysis Populations

5.3.1. All-Screened Population

The all-screened population includes all participants who signed the informed consent form.

The all-screened population will be used for the summary of analysis populations.

5.3.2. Full Analysis Set

The FAS includes all participants enrolled in the study who received at least 1 dose of INCB050465.

The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and all efficacy data.

5.3.3. Safety Population

The safety population includes all enrolled participants who received at least 1 dose of INCB050465.

All safety analyses will be conducted using the safety population.

[redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of planned tables, figures, and listings. Sample data displays are included in a separate document.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics will be summarized and listed for the FAS: age, sex, race, ethnicity, geographic region, weight, height, and BMI. Eastern Cooperative Oncology Group performance status at baseline will be summarized and listed for the FAS.

6.1.2. Disease History

Time since diagnosis, initial cytogenetics/expression analysis, current cytogenetics/expression analysis, initial Ann Arbor stage, current Ann Arbor stage, initial presence of B-symptoms, current presence of B-symptoms, current MIPI risk category, bone marrow involvement (yes vs no), bulky disease at baseline (longest diameter ≥ 10 cm vs 5-< 10 cm, vs < 5 cm) at baseline by the IRC, and relapsed/refractory status to the most recent prior therapy will be summarized and listed for all participants in the FAS. Date of tumor marker tests and test results will be listed.

Time since diagnosis will be calculated as:

Time since diagnosis (years) = (Day 1 date – date of diagnosis + 1) / 365.25.

6.1.3. Prior Therapy

Number of prior systemic cancer therapy regimens will be summarized for all participants in the FAS. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. Number and percentage of participants with each drug will be summarized by WHO drug class and WHO drug PT. Regimen name, component drugs, start and stop date, route of the medication, best response, reason for discontinuation, and date of relapse/progression will be listed.

Number of participants who received prior radiation will be summarized for the FAS. Anatomical location of the administration, start and stop date, and total dose will be listed.

Number of participants who had prior surgery or surgical procedure for the cancer treatment will be summarized for the FAS. Date and description of the surgery/procedure will be listed.

Number of participants who had hematopoietic stem cell transplant will be summarized for the FAS. Date of transplant, type of transplant, source of cells, line of therapy, best response, date of relapse/progression, regimen name, and drug used with the transplant will be listed.

6.1.4. Medical History

Medical history will be coded to SOC and PT using MedDRA coding dictionary. For participants in the FAS, medical history will be summarized by SOC and PT and listed.

6.2. Disposition of Participants

The number and percentage of participants who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, and who withdrew from the study with a primary reason for withdrawal will be summarized and listed for the FAS.

The number of participants enrolled by country and site will also be provided for the FAS.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be summarized and listed for the FAS.

6.4. Exposure

For participants in the safety population, exposure to INCB050465 will be summarized descriptively as the following:

- **Duration of treatment (days)**: Date of last dose – date of first dose + 1.
- **Duration of treatment during the initial QD dosing period (days)**: Date of last dose during initial QD dosing period – date of first dose + 1.
- **Duration of treatment during the maintenance dosing period (days)**: Date of last dose – date of first dose during the maintenance dosing period + 1. Crossover participants who switched to the selected treatment regimen after the start of the maintenance dosing period will be summarized in a separate group (ie, Crossover).
- **Average reported daily dose during the initial QD dosing period (mg/day)**: Total reported dose taken during initial QD dosing period (mg) / duration of treatment during the initial QD dosing period (days).
- **Average reported daily dose during the maintenance dosing period (mg/day)**: Total reported dose taken during the maintenance dosing period (mg) / duration of treatment during the maintenance dosing period (days). Crossover participants who switched to the selected treatment regimen after the start of the maintenance dosing period will be summarized in a separate group (ie, Crossover).
- **Dose modifications:** Number of participants who had dose reduction and interruption will be summarized. The number of dose reductions and the number of interruptions for each participant will be summarized.

6.5. Study Drug Compliance

For participants in the safety population, overall compliance (%) for INCB050465 will be calculated for all participants as

compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dosing eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. Number and percentage of participants in the FAS population with each prior and concomitant medication will be summarized by WHO drug class and WHO drug PT.

7. EFFICACY

Appendix A provides a list of planned tables, figures, and listings. Sample data displays are included in a separate document.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Response Assessment

An objective assessment of disease status is required at baseline (screening) using the CT-based response criteria of the Lugano Classification (Cheson et al 2014). Disease status will be subsequently assessed by CT or MRI every 8 weeks through Week 24, then every 12 weeks through Week 96, and then every 24 weeks thereafter until disease progression.

Bone marrow examination is required as a baseline assessment at screening except for reasons provided in Section 7.6.2 of the Protocol. If disease is present in bone marrow at baseline, a bone marrow examination will be required to confirm CR or may be performed as clinically indicated. If the bone marrow does not have lymphoma involvement at baseline, a repeat marrow examination is not required to confirm indication of CR on imaging.

Sites will use the CT-based response criteria of the Lugano Classification (Cheson et al 2014) to assess response to treatment locally. At each postbaseline disease assessment, response will be collected in the eCRF as CR, PR, SD, PD, or NE.

All imaging will be submitted to the IRC. Imaging data and applicable clinical data will be reviewed and response assessed using the CT-based response criteria of the Lugano Classification (Cheson et al 2014) by independent reviewers as described in the Independent Review Charter. An overall timepoint response at each postbaseline disease assessment, the best overall response, the date of initial response (if applicable), and the date of disease progression along with reason(s) of disease progression (if applicable) for each participant, considering radiographic data and clinical data, will be provided by the Clinical Reviewer. These data will be used in the analyses of related efficacy endpoints.

7.3. Analysis of the Primary Efficacy Parameter

The primary efficacy analyses will be conducted when all participants in the FAS who have achieved a response (ie, CR or PR) as determined by IRC have been followed approximately 12 months from the onset of first response.

7.3.1. Best Overall Response and Objective Response Rate

For responses determined by the IRC, the best overall response for each participant will be provided by the Clinical Reviewer. A participant is considered an objective responder if they have a best overall response of CR or PR.

The ORR is the proportion of objective responders. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR.

Best overall response as determined by the IRC will be summarized descriptively, and the ORR as determined by the IRC with 95% CIs will be calculated. Confidence intervals will be calculated based on the exact method for binomial distributions.

Because participants who switched to the selected treatment regimen after starting the maintenance dose received a mixture of the non-selected and selected maintenance regimens and could confound the efficacy evaluation of the non-selected treatment regimen, a sensitivity analysis of ORR as determined by IRC will be provided to summarize these crossover participants as a separate treatment regimen. In addition, the number of participants who achieved best overall response as determined by IRC after the time of crossover along with the best overall response data will be presented under this separate treatment regimen.

When applicable, sensitivity analysis of ORR as determined by the IRC may be provided excluding participants that do not have evaluable radiological images at baseline per the IRC.

7.3.2. Subgroup Analyses for Objective Response Rate

Subgroups will be formed based on the following participant characteristics and baseline variables:

- Age: < 65 years, ≥ 65 years
- Sex: male, female
- Race: White, others
- Geographic region: Europe, North America, rest of world
- Number of prior systemic therapy regimens: 1, 2-3
- Current Ann Arbor Staging: I-II, III-IV
- Bone marrow involvement at baseline: yes, no, unknown
- MIPI risk category: low (0-3), intermediate (4-5), high (6-11)
- ECOG performance status: 0, 1, 2

- Bulky disease at baseline: longest diameter ≥ 10 cm vs 5- < 10 cm, vs < 5 cm at baseline by IRC
- Relapsed/refractory status to the most recent prior therapy: relapsed, refractory, unknown

Subgroups may be further divided or combined based on emerging data. The ORR as determined by the IRC and its 95% exact binomial CIs will be provided for participants for each subgroup. A forest plot will be created to summarize the variability in ORRs as determined by the IRC for participants across subgroups.

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Duration of Response

Duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an objective response (ie, CR or PR), as determined by revised response criteria for lymphomas (Cheson et al 2014). For responses assessed by the IRC, the date of initial response and date of disease progression will be provided by the Clinical Reviewer for participants who have achieved best response of CR or PR. Censoring of DOR will follow the same algorithm as the censoring of PFS (see Section 7.4.3).

The total number of responders as determined by the IRC, the number of participants whose disease progressed as determined by the IRC or who died, and the number of participants censored will be summarized. The Kaplan-Meier estimate of median DOR as determined by the IRC and its 95% CIs will be provided, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

A sensitivity analysis of DOR will be performed where response assessments after the time of crossover will be excluded from the determination of DOR for participants who switched to the selected treatment regimen after starting the maintenance dose. Crossover participants who have not progressed at the time of crossover will be censored at the last valid radiologic assessment on/before the time of crossover. Participants who failed to achieve a response of CR or PR on/before the time of crossover will not be considered as responders for this analysis.

7.4.2. Complete Response Rate

Complete response rate is the percentage of participants with a best overall response of CR as defined by revised response criteria for lymphomas (Cheson et al 2014). For responses determined by the IRC, the best overall response for each participant will be provided by the Clinical Reviewer. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of CRR.

The CRR as determined by the IRC will be estimated with 95% CIs. Confidence intervals will be calculated based on the exact method for binomial distributions.

A sensitivity analysis of CRR will be provided to summarize participants who switched to the selected treatment regimen after starting the maintenance dose as a separate treatment regimen.

7.4.3. Progression-Free Survival

Progression-free survival is defined as the time from the date of the first dose of the study drug to the first documented disease progression as determined by revised response criteria for lymphomas (Cheson et al 2014), or death due to any cause, whichever occurs first. For response assessed by the IRC, date of disease progression will be provided by the Clinical Reviewer. Censoring for PFS will follow the algorithm outlined in Table 2, which is based on FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (2015) and Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

Table 2: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing) before the missed assessments

NE = not evaluable.

The total number of participants whose disease progressed as determined by the IRC or who died, and the number of participants censored will be summarized. The Kaplan-Meier estimate of median PFS as determined by the IRC and its 95% CIs will be provided, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Progression-free survival rates at 6, 12, 18, 24, and 36 months will also be provided with 95% CIs calculated using Greenwood's formula to estimate the standard error.

A sensitivity analysis of PFS will be performed where response assessments after the time of crossover will be excluded from the determination of PFS for participants who switched to the selected treatment regimen after starting the maintenance dose. Crossover participants who have not progressed at the time of crossover will be censored at the last valid radiologic assessment on/before the time of crossover.

7.4.4. Overall Survival

Overall survival is defined as the time from the date of the first dose of study drug to death due to any cause. For participants who are still alive at the time of the analysis, OS will be censored on the date the participant is last known to be alive.

The number of participants who died and the number of participants censored will be summarized. The Kaplan-Meier estimate of median OS and its 95% CIs will be presented with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Survival rates at 6, 12, 18, 24, and 36 months will also be provided with 95% CIs calculated using Greenwood's formula to estimate the standard error.

7.4.5. Best Percent Change in Target Lesion Size

For each participant with measurable lesions at baseline, target lesion sizes will be measured by the sum of the product of diameters of all target lesions. The best percent change from baseline, defined as the largest decrease in target lesion sizes during the study, will be summarized, and a waterfall plot of the best percent change will be generated using data from the IRC. Note that for participants who only have increases in target lesion sizes from baseline, the smallest increase will be considered as the best change from baseline. For the IRC, there will be 2 radiologic reviewers for each participant. An adjudication will be performed per the Independent Review Charter when Reviewers 1 and 2 disagree on the CT/MRI best overall response, or when best overall response is consistent and the date of initial response and/or the date of PD differ between Reviewers 1 and 2. The adjudicator will choose the read that he or she believes most accurately represents the adjudication parameter(s) in question. This is considered the "accepted read," and data from this reviewer will be used for the analysis. When there was no adjudication needed, data from Reviewer 1 will be used for the analysis. An indicator is provided to identify the read that is considered to be the accepted assessment in data from the IRC.

Best change in target lesion size as reported by the investigator will also be summarized as described above. Target lesions considered "too small to measure" will be assigned a default value of 5 mm × 5 mm for the purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm × 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or NE), then the overall sum of the product of diameters for target lesions will not be evaluable for that postbaseline timepoint.

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9. SAFETY AND TOLERABILITY

Appendix A provides a list of planned tables, figures, and listings. Sample data displays are included in a separate document.

9.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few participants.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug and within 30 days of the last administration of study drug regardless of starting new anti-lymphoma therapy. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE. CTCAE v4.03 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

9.2.2. Adverse Events of Special Interest

The number of participants who experienced TEAEs of special interest listed below will be summarized by maximum severity.

- Colitis
- Diarrhea
- Exfoliative dermatitis

- Febrile neutropenia
- Rash
- Intestinal perforation
- Pneumonitis
- Pneumonia
- PJP infection
- CMV infection
- Herpes simplex
- Varicella zoster virus infection

The time to onset of a TEAE is defined as the interval between the date of first dose of study drug and the date of the first occurrence of a TEAE. Participants who have not experienced a TEAE at the time of analysis will be right-censored at the earlier of 30 days after the last dose date and date of last study visit through the end of safety follow-up. If participants have missing or partial last dose dates of study drug or onset date of a TEAE, the partial or missing dates will be handled using the rules explained in Section 4.1.4.

Summaries of time to onset of new or worsening Grade 3 or higher AEs will be provided using descriptive statistics and the life-table method for rash, colitis, diarrhea, febrile neutropenia, pneumonia, herpes simplex, and varicella zoster virus infection. In addition, summaries of time to onset of new or worsening AEs of any grade will be provided using descriptive statistics and the life-table method for colitis, diarrhea, exfoliative dermatitis, intestinal perforation, pneumonia, pneumonitis, PJP infection, CMV infection, herpes simplex, and varicella zoster virus infection. Kaplan-Meier plots of time to onset of new or worsening Grade 3 or higher AEs will be provided for rash, colitis, and diarrhea. In addition, Kaplan-Meier plots of time to onset of new or worsening AEs of any grade will be provided for colitis and diarrhea.

Descriptive statistics of time to onset of these TEAEs of special interest are based on all participants who have experienced a TEAE at the time of analysis. To summarize these TEAEs of special interest using the life-table method, the effective sample size is defined as the number of participants at the beginning of the interval minus half the participants censored in the interval. The conditional proportion is calculated as the number of first events divided by the effective sample size in the interval.

The longest duration of a TEAE of any grade is defined as the longest interval between the date of occurrence of a TEAE and the date of resolution. The longest duration of a Grade 3 or higher TEAE is defined as the longest interval between the date of occurrence of a Grade 3 or higher TEAE and the date of improvement to Grade 2 or lower. If participants have missing or partial onset/end date of a TEAE, the partial or missing dates will be handled using the rules explained in Section 4.1.4. Participants who have missing end date of a TEAE at the time of analysis will be right-censored using the following algorithm:

- If the TEAE is serious, then the participant will be censored at the earlier date of data cutoff, study discontinuation and death.

- If the TEAE is not serious,
  - If the participant is ongoing with study treatment, then the participant will be censored at the data cutoff date, OR
  - If the participant discontinued treatment, then the participant will be censored at date of safety follow-up visit, or 35 days after the end of treatment visit (or after the last dose if the end of treatment visit was not performed), whichever is later; the censored date will be truncated by the earlier date of data cutoff, study discontinuation, and death if beyond.

Longest duration of new or worsening Grade 3 or higher colitis, diarrhea, rash, and febrile neutropenia will be summarized. In addition, longest duration of new or worsening AEs of any grade will be summarized for colitis, diarrhea, and rash.

The total number of participants whose TEAE of any grade resolved or whose Grade 3 or higher TEAE improved to Grade 2 or lower, and the number of participants censored will be summarized. The Kaplan-Meier estimate of median time to resolution/improvement and its 95% CIs will be provided, with the CIs calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997). Resolution/improvement rates at selected timepoints will also be provided with 95% CIs calculated using Greenwood's formula to estimate the standard error.

TEAEs of special interest to be summarized may be adjusted based on emerging data.

9.2.3. Adverse Event Summaries

Overall summaries of TEAEs by treatment regimen will be provided during the INCB050465 initial QD dosing period, maintenance dosing period, and overall period (ie, all TEAEs regardless of the timing of occurrence). These summaries will include the following:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any TEAEs related to INCB050465
- Number (%) of participants reporting any Grade 3 or higher TEAEs related to INCB050465
- Number (%) of participants reporting any serious TEAEs related to INCB050465
- Number (%) of participants who had TEAE with fatal outcome
- Number (%) of participants with INCB050465 dose reductions because of TEAEs
- Number (%) of participants who temporarily interrupted INCB050465 because of TEAEs
- Number (%) of participants who permanently discontinued INCB050465 because of TEAEs

The following summaries will be produced for TEAEs during the overall period by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of TEAEs by PT and maximum severity in decreasing order of frequency
- Summary of Grade 3 or higher TEAEs by SOC and PT
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency
- Summary of serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in descending order of frequency
- Summary of INCB050465 treatment-related TEAEs by SOC and PT
- Summary of INCB050465 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of INCB050465 treatment-related TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or higher INCB050465 treatment-related TEAEs by SOC and PT
- Summary of INCB050465 treatment-related serious TEAEs by SOC and PT
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to INCB050465 dose reduction by SOC and PT
- Summary of TEAEs leading to INCB050465 dose interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of INCB050465 by SOC and PT
- Summary of selected TEAEs of special interest by maximum severity
- Summary of time to onset of selected TEAEs of special interest
- Summary of time to onset of selected TEAEs of special interest: life-table method
- Summary of longest duration of selected TEAEs of special interest

The following supporting summaries will be produced for TEAEs during the INCB050465 initial QD dosing period and the maintenance dosing period by MedDRA term. For the supporting summaries during the maintenance dosing period, participants who cross over to the selected treatment regimen after the start of the maintenance dosing period will be summarized in a separate group (ie, Crossover):

- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by PT and maximum severity in decreasing order of frequency
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency

- Summary of serious TEAEs by PT in descending order of frequency
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to discontinuation of INCB050465 by SOC and PT

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, the value from the central laboratory has priority over the value from the local laboratory. Thereafter, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v4.03.

9.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple laboratory nonmissing values for a participant's particular test at a scheduled visit, central laboratory values have higher priority over local laboratory values. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, line graphs will be provided for ALT, AST, hemoglobin, platelet counts, leukocytes, neutrophils, and lymphocytes.

Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum postbaseline severity.

9.3.3. Potential Hy's Law Events

Participants with elevated ALT or AST > 3 × ULN range and alkaline phosphatase < 2 × ULN range accompanied by total bilirubin > 2 × ULN range at the same visit will be listed by treatment group.

9.3.4. Worsening Laboratory Events of Special Interest

Laboratory events of special interest are listed below.

- ALT increased
- AST increased
- Absolute neutrophil count decreased

The time to onset of a worsening laboratory event is defined as the interval between the date of first dose of study drug and the date of the first occurrence of CTC grade worse than baseline for the laboratory event. Participants who have not experienced a worsening laboratory event at the time of analysis will be right-censored at the last postbaseline study visit with nonmissing CTC grade of the laboratory event.

Time to onset of worsening Grade 3 or 4 laboratory events of special interest will be summarized using descriptive statistics and the life-table method as described in Section 9.2.2, and the Kaplan-Meier plot of time to onset of worsening Grade 3 or 4 absolute neutrophil count decreased will be provided. Laboratory events of special interest to be summarized may be adjusted based on emerging data.

9.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, body temperature, respiratory rate, and weight will be summarized descriptively.

Normal ranges for vital sign values are defined in Table 4. The abnormal values for participants exhibiting vital sign abnormalities will be listed along with their assigned treatment regimen. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 4: Normal Ranges for Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38°C	≥ 35°C
Respiratory rate	≤ 24 breaths/min	≥ 12 breaths/min

9.5. Electrocardiograms

Twelve-lead ECGs including PR, QRS, QT, QTcB, QTcF, and RR intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percent change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of INCB050465.

Normal ranges for ECG values are defined in Table 5. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment regimen. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT, QTcB, and QTcF values, defined as absolute values > 450 milliseconds or change from baseline > 30 milliseconds, will be summarized.

Table 5: Normal Ranges for Electrocardiogram Values

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
QRS	≤ 120 ms	≥ 50 ms
QT	≤ 500 ms	≥ 300 ms
QTcB, QTcF	≤ 450 ms	≥ 295 ms
RR	≤ 1330 ms	≥ 600 ms

QTcB = Bazett's correction; QTcF = Fridericia's correction.

10. INTERIM ANALYSES

An interim futility analysis is planned for each of the cohorts when 30 participants have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death.

Cohort 1 will be terminated for futility if ≤ 3 of the 30 participants responded (ie, CR or PR) based on assessments provided by the IRC; otherwise, the study for Cohort 1 will continue. The probability of stopping at interim for futility is 0.51 when the true response rate is 12%, 0.12 when the true response rate is 20%, or 0.02 when the true response rate is 28%.

Cohort 2 will be terminated for futility if ≤ 10 of the 30 participants responded (ie, CR or PR) based on assessments provided by the IRC; otherwise, the study for Cohort 2 will continue. The probability of stopping at interim for futility is 0.29 when the true response rate is 40%, 0.05 when the true response rate is 50%, or 0.003 when the true response rate is 60%.

An IDMC will be charged with evaluating interim futility results. The IDMC will consist of clinicians and an independent statistician. The IDMC will make recommendations to the sponsor at the planned interim futility analysis for both cohorts. The process by which the IDMC will make recommendations and decisions will be documented in the IDMC Charter. Additional operational details of the interim analyses, including tables, figures, and listings provided to the IDMC, will be provided in the IDMC Charter.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 6.

Table 6: Statistical Analysis Plan Versions

SAP Version	Date
Original	04 FEB 2019
Amendment 1	27 AUG 2020
Amendment 2	28 JAN 2021

11.1. Changes to Protocol-Defined Analyses

The PP population was removed from the planned analysis. For a single arm, open-label study, the determination of participants to be excluded from the PP population is post hoc and may not be done objectively; thus, analysis based on this population may not be meaningful.

11.2. Changes to the Statistical Analysis Plan

Amendment 2 (28 JAN 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to comply with responses to comments provided by FDA regarding the Statistical Analysis Plan Amendment 1.

- Section 6.4 was updated to include the summary for the number of dose reductions and the number of dose interruptions of each participant.
- Section 7.3 was updated to include the timing of primary efficacy analysis.
- Section 7.3.1 was updated to include a sensitivity analysis of ORR that summarizes participants who switched to the selected dose after starting the maintenance dose in a separate treatment regimen and to include an additional analysis on the number of participants who achieved best overall response after the time of crossover along with the best overall response data for this separate treatment regimen.
- Section 7.3.2 was revised to update the subgroup analysis by number of prior systemic therapy regimens at 1 vs 2-3, because historical clinical evidence suggests that third-line or later participants may have a poorer outcome compared with second-line participants in MCL.
- Section 7.4.1 and Section 7.4.3 were updated to included sensitivity analyses where response assessments after the time of crossover will be excluded from the determination of DOR and PFS for participants who switched to the selected treatment regimen after starting the maintenance dose.
- Section 7.4.2 was updated to include a sensitivity analysis of CRR by summarizing participants who switched to the selected dose after starting the maintenance dose in a separate treatment regimen.

- Section 9.2.1 was modified to clarify how AEs that occur after new anti-lymphoma therapy will be assessed.
- **Incorporation of minor changes.** Other minor changes have been incorporated throughout the SAP and are noted in the redline version of the amendment.

Amendment 1 (27 AUG 2020)

- Section 3 was revised to state that 40 additional participants will be added to Cohort 2 rather than 30 additional participants, thus increasing the total number of participants in Cohort 2 from 90 to 100. This change is to comply with recommendations from FDA to achieve a sufficient number of participants in Cohort 2 to support registration.
- Section 4.1.4 was updated to include details of rules for handling partial/missing onset or end date of TEAEs in the calculation of time to onset or duration of a TEAE. Rules for partial/missing date of last dose were updated to include details for when both month and day are missing.
- Section 5.2 was modified to provide details regarding how crossover participants will be summarized.
- Section 5.3 was updated to remove the efficacy evaluable analysis set and use the FAS for all analyses of efficacy data. This change is to comply with comments from FDA that any participants who received at least 1 dose should be included in the efficacy analyses for a single-arm trial. The all-screened population was added for the summary of analysis populations.
- Section 6.1.1 was modified to add geographic region to the summary of demographic and baseline characteristics because it is one of the subgroups used for analyses on ORR.
- Section 6.1.2 was modified to remove summaries of tumor markers but only keep listings. Relapsed/refractory status to the most recent prior therapy was added to the summary table of disease history because the response to last regimen before entering the study may be a prognostic factor for clinical outcomes.
- Section 6.2 was modified to add summaries of participants who are ongoing with treatment or still in the study.
- Section 6.4 was modified to change the calculations of duration of treatment and average dose during the maintenance dosing period because Group B with 2.5 mg QD was selected as the maintenance dose.
- Section 7.3.1 was modified to replace the efficacy evaluable analysis set with the full analysis set. This change is to align with Protocol Amendment 7 dated 30 JAN 2020 and include all treated participants in the efficacy analyses to comply with comments from FDA.
- Section 7.3.2 was modified to add "unknown" as a category for bone marrow involvement at baseline. Relapsed/refractory status to the most recent prior therapy was added to the subgroup analysis because the response to last regimen before entering the study may be a prognostic factor for clinical outcomes.

- Section 7.4.3 was modified to update references of censoring for PFS.
- Section 9.2.2 was updated to include details of analyses on time to onset of selected TEAEs of special interest. Summaries of longest duration of selected TEAEs of special interest were added to have a better understanding of the safety profile in terms of duration of class-effect AEs as well as AEs influenced by treatment regimens. "Grade 2 or higher" was changed to "Grade 3 or higher" for time to onset summary of rash. This change was made to be consistent with other PI3K inhibitors, which highlighted more severe cutaneous reactions graded as Grade 3 or higher in the labeling. "Herpes simplex virus infection" was changed to "herpes simplex" based on the MedDRA coding dictionary as a broader term. Exfoliative dermatitis was added to the list of TEAEs of special interest.
- Section 9.2.3 was updated to include summary of TEAEs by PT and maximum severity in decreasing order of frequency, summary of longest duration of selected TEAEs of special interest, and additional supporting summaries during the INCB050465 initial QD dosing period and the maintenance dosing period, which will provide supportive data of the safety profile of the maintenance dose. Summary of nonserious TEAEs by SOC and PT was removedbecause it will not be used for the clinical study report but will be provided for result disclosure.
- Section 9.3.2 was modified to include ALT and AST in the line graphs as additional supportive analyses for laboratory events of special interest.
- Section 9.3.3 was added to identify potential Hy's law events to better monitor liver toxicity.
- Section 9.3.4 was updated to align with the analysis plan for adverse events of special interest. Summary of worsening of laboratory events of special interest was removed because this is covered by the summary of worsening of laboratory abnormalities.
- Section 9.5 was updated to change the high threshold of QTcF and QTcB interval from 460 to 450 milliseconds for the purpose of analysis. This change is to comply with the categories outlined in FDA Guidance for Industry (E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) used to characterize outliers in QTc values.

12. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068.

Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York, NY: Springer; 1997.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report for Cohort 1 and Cohort 2. Outputs from Cohort 1 will have ".1" at the end of the numbering. Outputs from Cohort 2 will have ".2" at the end of the numbering. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.9.

The lists of tables, figures, listings and the shells are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1.1	Analysis Populations	All-Screened	X
1.1.2	Summary of Participant Disposition	FAS	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	FAS	X
1.1.4	Summary of Protocol Deviations	FAS	X
1.2.1	Summary of Demographics and Baseline Characteristics	FAS	X
1.3.1	Summary of Baseline Disease Characteristics	FAS	X
1.3.2	Summary of Prior Cancer Therapy	FAS	
1.3.3	Summary of Prior Systematic Cancer Therapy by WHO Drug Class and Preferred Term	FAS	
1.4.1	Summary of Prior Medications	FAS	X
1.4.2	Summary of Concomitant Medications	FAS	X
1.5.1	Summary of General Medical History	FAS	X
Efficacy			
2.1.1	Summary of Best Overall Response and Objective/Complete Response Rate as Determined by Independent Review Committee	FAS	
2.1.2	Summary of Best Overall Response and Objective/Complete Response Rate as Reported by Investigator	FAS	
2.1.3	Summary of Best Overall Response and Objective Response Rate as Determined by Independent Review Committee by Subgroup	FAS	
2.2.1	Summary of Duration of Response as Determined by Independent Review Committee	FAS	
2.2.2	Summary of Duration of Response as Reported by Investigator	FAS	
2.2.3	Summary of Progression-Free Survival as Determined by Independent Review Committee	FAS	
2.2.4	Summary of Progression-Free Survival as Reported by Investigator	FAS	
2.2.5	Summary of Overall Survival	FAS	
2.2.6	Summary of Best Change in Target Lesion Size as Determined by Independent Review Committee	FAS	

Table No.	Title	Population	Standard
2.2.7	Summary of Best Change in Target Lesion Size as Reported by Investigator	FAS	
[redacted]			
2.4.1	Summary of Best Overall Response and Objective/Complete Response Rate as Determined by Independent Review Committee – Crossover as a Separate Treatment Group	FAS	
2.4.2	Summary of Best Overall Response and Objective/Complete Response Rate as Reported by Investigator – Crossover as a Separate Treatment Group	FAS	
2.4.3	Summary of Best Overall Response as Determined by Independent Review Committee for Crossover Participants	FAS	
2.4.4	Summary of Best Overall Response as Reported by Investigator for Crossover Participants	FAS	
2.4.5	Summary of Duration of Response as Determined by Independent Review Committee – Censoring Crossover Participants	FAS	
2.4.6	Summary of Duration of Response as Reported by Investigator – Censoring Crossover Participants	FAS	
2.4.7	Summary of Progression-Free Survival as Determined by Independent Review Committee – Censoring Crossover Participants	FAS	
2.4.8	Summary of Progression-Free Survival as Reported by Investigator – Censoring Crossover Participants	FAS	
Safety			
3.1.1	Summary of Exposure and Compliance	Safety	
3.1.2	Summary of Exposure and Average Daily Dose During Initial QD Dosing Period	Safety	
3.1.3	Summary of Exposure and Average Daily Dose During Maintenance Dosing Period	Safety	
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X

Table No.	Title	Population	Standard
3.2.7	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.10	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.11	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.12	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X
3.2.14	Summary of Grade 3 or Higher Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.15	Summary of Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.16	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.18	Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.19	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.20	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.25	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum Severity in Decreasing Order of Frequency	Safety	
3.2.26	Summary of Selected Treatment-Emergent Adverse Events of Special Interest by Maximum Severity	Safety	
3.2.27	Summary of Time to Onset of Selected Treatment-Emergent Adverse Events of Special Interest	Safety	
3.2.28	Summary of Time to Onset of Selected Treatment-Emergent Adverse Events of Special Interest : Life-Table Method	Safety	
3.2.29	Summary of Longest Duration of Selected Treatment-Emergent Adverse Events of Special Interest	Safety	
3.3.1.1	Summary of Laboratory Values - Hematology	Safety	X
3.3.1.2	Summary of Laboratory Values - Chemistry	Safety	X
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTC Grade - To the Worst Abnormal Value	Safety	X
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTC Grade - To the Worst Abnormal Value	Safety	X

Table No.	Title	Population	Standard
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Safety	X
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Safety	X
3.3.6	Time to Onset of Treatment-Emergent Worsening of Laboratory Events of Special Interest	Safety	
3.3.7	Time to Onset of Treatment-Emergent Worsening of Laboratory Events of Special Interest: Life-Table Method	Safety	
3.4.1	Summary of Systolic Blood Pressure	Safety	X
3.4.2	Summary of Diastolic Blood Pressure	Safety	X
3.4.3	Summary of Pulse	Safety	X
3.4.4	Summary of Respiratory Rate	Safety	X
3.4.5	Summary of Body Temperature	Safety	X
3.4.6	Summary of Weight	Safety	X
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X
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