Official Title:	**A Phase 2, Open-Label, 2-Cohort Study of INCB050465, a PI3Kδ Inhibitor, in Subjects with Relapsed or Refractory Marginal Zone Lymphoma with or Without Prior Exposure to a BTK Inhibitor (CITADEL-204)**
NCT Number:	NCT03144674
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Clinical Study Protocol

INCB 50465-204

A Phase 2, Open-Label, 2-Cohort Study of INCB050465, a PI3Kδ Inhibitor, in Subjects With Relapsed or Refractory Marginal Zone Lymphoma With or Without Prior Exposure to a BTK Inhibitor (CITADEL-204)

Product:	**INCB050465**
IND Number:	**121,474**
EudraCT Number:	**2017-000970-12**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**22 MAR 2017**
Protocol (Version 0-UK):	**26 SEP 2017**
Amendment (Version) 1:	**24 JAN 2018**
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Amendment (Version) 2:	**18 JUL 2018**
Amendment (Version) 3:	**07 DEC 2018**
Amendment (Version) 4:	**23 DEC 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-204 Protocol Amendment 4 (Version 4 dated 23 DEC 2019) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB050465

Title of Study: A Phase 2, Open-Label, 2-Cohort Study of INCB050465, a PI3Kδ Inhibitor, in Subjects With Relapsed or Refractory Marginal Zone Lymphoma With or Without Prior Exposure to a BTK Inhibitor (CITADEL-204)

Protocol Number: INCB 50465-204 | **Study Phase:** 2

Indication: Marginal zone lymphoma

Objectives	Endpoints
Primary	
To assess the efficacy of INCB050465 in terms of objective response rate (ORR) in subjects with marginal zone lymphoma (MZL) that is relapsed or refractory after at least 1 systemic treatment regimen.	ORR defined as the percentage of subjects with a complete response (CR) or partial response (PR) as determined by Independent Review Committee (IRC) assessment of response according to computed tomography (CT)-based response criteria for lymphomas.
Secondary	
To assess duration of response (DOR).	DOR defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among subjects who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess complete response rate (CRR).	CRR defined as the percentage of subjects with a CR as defined by response criteria for lymphomas, as determined by an IRC.
To assess progression-free survival (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 overall survival (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 adverse events (AEs), 12-lead electrocardiograms (ECGs), chemistry and hematology laboratory values, vital signs, and physical examinations.

[redacted]

Overall Study Design: This is a Phase 2, open-label study designed to evaluate the safety and efficacy of 2 INCB050465 treatment regimens in subjects diagnosed with relapsed or refractory MZL. The study was originally planned to enroll 2 cohorts: Cohort 1 for subjects who were previously treated with a Bruton's tyrosine kinase (BTK) inhibitor (n = 60) and Cohort 2 for subjects who are naive to BTK inhibitor (n = 60).

Per Protocol Amendment (Version) 3, only subjects who have not received a prior BTK inhibitor (ie, Cohort 2) will continue to be enrolled. Cohort 1, which comprises subjects who have received prior ibrutinib, will be closed to further enrollment with Protocol Amendment (Version) 3.

Subjects already enrolled in Cohort 1 will continue to receive study treatment per the protocol, and their data will be reported and analyzed separately from subjects in Cohort 2.

Subjects in Cohort 2 (n = 60) will be further allocated to 1 of the 2 study treatment regimens as follows:

- Treatment A: INCB050465 20 mg once daily (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.

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

An interim futility analysis is planned when the first 30 subjects in Cohort 2 have been treated and evaluated for response or permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Cohort 2 will be terminated for futility if ≤ 10 of the 30 subjects have responded (ie, CR or PR) based on assessments provided by the IRC. A timely assessment of response will be performed to avoid the risk of overenrollment.

To better understand the safety and efficacy of INCB050465, an additional 30 subjects will be enrolled into one of the two treatment regimens (A or B) being evaluated in this Study. The treatment regimen will be selected after enrollment is completed for Cohort 2 (ie, 60 subjects enrolled) and after evaluation of emerging safety and efficacy data from this and other monotherapy studies of INCB050465 in NHL. Once a treatment regimen is selected, the non-selected treatment regimen will be closed to further enrollment. Subjects receiving the non-selected treatment regimen may switch to the selected treatment regimen or remain on their current treatment regimen, provided the subject has not met study-treatment withdrawal criteria and there are no safety concerns for their current treatment regimen. There will be no re-baselining for subjects who switch treatment regimens and all subjects will continue to follow the same assessment schedule.

Study Population: Subjects with histologically confirmed MZL, including extranodal, nodal, and splenic subtypes, who previously received 1 or more lines of systemic therapy, including at least 1 anti-CD20 antibody, with documented progression or documented failure to achieve CR or PR after the most recent systemic treatment regimen.

Key Inclusion Criteria:

- Men and women, aged 18 or older (except in South Korea, aged 19 or older).
- Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the longest transverse diameter (LDi) and ≥ 1.0 cm in the longest perpendicular diameter as assessed by CT or magnetic resonance imaging (MRI).
  - Subjects with splenic MZL who do not meet the radiographically measurable disease criteria described herein are eligible for participation provided that bone marrow infiltration of MZL is histologically confirmed.

- Subjects must be willing to undergo an incisional or excisional lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue.
  - Subjects with splenic MZL who do not have a tumor to biopsy or archival tumor tissue are eligible for participation provided subject is willing to undergo a bone marrow biopsy or provide an archival bone marrow biopsy that was obtained since completion of last therapy and within two years before the date of the first dose of study treatment.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

Key Exclusion Criteria:

- Evidence of diffuse large B-cell transformation.
- History of central nervous system lymphoma (either primary or metastatic) or leptomeningeal disease.
- Prior treatment with idelalisib, other selective PI3Kδ inhibitors, or a pan-PI3K inhibitor.
- Allogeneic stem cell transplant within the last 6 months, or autologous stem cell transplant within the last 3 months before the date of the first dose of study treatment.
- Active graft versus host disease.
- Liver disease:
  - Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.

INCB050465 Study Dosage, and Mode of Administration: INCB050465 will be administered orally at a dose of 20 mg QD for 8 weeks followed by 20 mg once weekly (Treatment A) or 20 mg QD for
8 weeks followed by 2.5 mg QD (Treatment B).

Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Required Concomitant Medications: All subjects must receive prophylaxis against *Pneumocystis jirovecii* pneumonia from the start of study treatment and should continue for at least 2 to 6 months after the last dose of study treatment.

Study Schedule/Procedures: Subjects will undergo screening assessments, including physical examination; laboratory tests, including pregnancy and serology tests; an ECG; and a bone marrow examination to determine eligibility. During the treatment period, subjects will be monitored for safety through disease-specific physical examinations, including vital signs, ECOG performance status, assessment of AEs, ECGs, and laboratory assessments every 4 weeks through Week 48 and then every 12 weeks thereafter; hematology will be assessed every 2 weeks for the first 8 weeks. Disease status will be assessed (using the same modality [CT/MRI] from screening) every 8 weeks through Week 24, then every 12 weeks through Week 96, and then every 24 weeks thereafter until disease progression. [redacted] Subjects withdrawn from study treatment for reasons other than disease progression will be followed for disease status until either radiologic disease progression, the start of a new anticancer therapy, consent withdrawal, or death (whichever occurs first). After permanently discontinuing study treatment, subjects will be followed every 12 weeks for subsequent anticancer therapies and survival.

Estimated Duration of Participation: Subject participation from screening through follow-up is expected to average approximately 25 months, which includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject is receiving benefit, tolerating the regimen, and has not met withdrawal criteria (approximately 52 weeks).

- A safety follow-up period lasting 30 to 35 days.
- A disease and survival follow-up period until the end of the study.

At the end of the study, subjects who have completed at least 24 months of study participation (starting from first dose of INCB050465), who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

Estimated Number of Subjects: Approximately 90 subjects who have not received prior BTK inhibitor will be enrolled into Cohort 2. Cohort 1, which comprises subjects who have received prior ibrutinib, will be closed to further enrollment with Protocol Amendment (Version) 3.

Principal Coordinating Investigators:
US: [redacted], MD, [redacted], MI, USA
EU: [redacted], MD, [redacted], United Kingdom

Statistical Methods: Data from Cohort 1 and Cohort 2 will be analyzed separately. There will not be any statistical comparison between Cohort 1 and Cohort 2, and there will not be multiplicity adjustment between the cohorts.

Sample Size:

Cohort 1: Will be closed to further enrollment with Protocol Amendment (Version) 3.

Cohort 2: Up to 90 subjects will be enrolled. If the true ORR is 60%, then there is approximately 90% or 96% probability of observing the lower bound of the 95% CI of ORR $\geq$ 40% with 60 or 90 subjects, respectively.

Primary Analysis: For each of the 2 cohorts, the ORR as determined by the IRC and its 95% exact binomial CIs will be calculated.

Secondary Analyses: For each of the 2 cohorts, the Kaplan-Meier estimation of median DOR, PFS (per IRC), and OS will be presented with respective 95% CIs. The CRR as determined by the IRC and its 95% exact binomial CIs will be calculated. Best percentage change in target lesion size from baseline will be summarized descriptively. All safety data, including AEs, laboratory data, vital signs, and ECGs, will be summarized descriptively.

Level of Significance: There will not be any statistical comparison between the 2 cohorts. Within each of the 2 cohorts, 2-sided 95% CIs will be reported for all analyses when appropriate.

Interim Analysis: An interim futility analysis is planned for Cohort 2 when 30 subjects have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Cohort 2 will be terminated for futility if $\leq$ 10 of the 30 subjects responded (ie, CR or PR) based on assessments provided by the IRC.

Data Monitoring Committee: An Independent Data Monitoring Committee (IDMC) will be established and will review data at predetermined intervals as specified in the IDMC charter.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response
CRR	complete response rate
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization

Abbreviation	Definition
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IN	Investigator Notification
irAE	immune-related adverse event
IRB	institutional review board
IRC	Independent Review Committee
IWRS	interactive web response system
LDi	longest transverse diameter
MALT	mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
[redacted]	[redacted]
NHL	non-Hodgkin's lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PJP	*Pneumocystis jirovecii* pneumonia
[redacted]	[redacted]
[redacted]	[redacted]response
PO	orally
PP	per protocol
PR	partial response
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
[redacted]	[redacted]
WBC	white blood cell

1. INTRODUCTION

1.1. Marginal Zone Lymphoma

In the United States, NHL is the seventh most common cancer affecting adults. Between 1975 and 2013, the incidence of NHL in the United States nearly doubled, and more than 72,000 new cases are expected to be diagnosed in 2016 (Lymphoma Research Foundation 2017a). In Europe, NHL is the 11th most common cancer, with approximately 93,500 new cases diagnosed in 2012 (3% of the total). Non-Hodgkin lymphoma is the 10th most common cancer worldwide, with nearly 386,000 new cases diagnosed in 2012 (3% of the total; Ferlay et al 2013).

Marginal zone lymphomas, a group of indolent (slow-growing) NHL B-cell lymphomas, account for approximately 10% of all histologically diagnosed NHL cases in western countries (Cuneo and Castoldi 2006). The average age at diagnosis is 60 years, and it is slightly more common in women than in men (Lymphoma Research Foundation 2017b).

Marginal zone lymphomas originate from memory B lymphocytes normally present in a distinct microanatomic compartment called the "marginal zone" of the secondary lymphoid follicles (Zinzani 2012). The subtypes of MZL share a similar immunophenotype that are positive for the B-cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and usually CD23 (Swerdlow et al 2016).

The latest lymphoma classification identifies 3 subtypes of MZL according to the involved site and characteristic molecular findings (Swerdlow et al 2016):

- Extranodal MZL of MALT type,
- Nodal MZL, and
- Splenic MZL.

1.1.1. Extranodal MZL (MALT)

Extranodal MZL is the most common form of MZL accounting for two-thirds of all cases per year and composes approximately 5% of all NHLs (Lymphoma Research Foundation 2017b). Extranodal MZL (MALT) differs from splenic and nodal MZL due in part to its involvement in epithelial tissues, including the stomach, lungs, salivary glands, small bowel, thyroid, and lachrymal glands. Extranodal MZL is hypothesized to arise from memory B cells with the ability to differentiate into marginal zone cells and plasma cells (Novak et al 2011). Four recurrent chromosomal translocations have been specifically associated with the pathogenesis of extranodal MZLs (Bertoni and Zucca 2006):

- t(11;18)(q21;q21),
- t(1;14)(p22;q32),
- t(14;18)(q32;q21), and
- t(3;14)(p14.1;q32).

The oncogenic activity of t(11;18), t(14;18), and t(1;14) is attributable to the pathophysiologic increases in the activation of NF-κB through the BCL10/MALT1 signaling complex, thereby enhancing the proliferation and survival of extranodal MZL cells (Sagaert et al 2007). The other

known translocation, t(3;14)(p13;q32), fuses the FOXP1 gene on chromosome 3 to the IgH gene and results in increased nuclear levels of the FOXP1 transcription factor (Wlodarska et al 2005).

Increasing evidence suggests that extranodal MZL may be related to chronic immune reactions caused by bacterial (ie, *Helicobacter pylori*-induced chronic gastritis and *Campylobacter psittaci*), viral (ie, HCV infection), or autoimmune stimuli (ie, history of Sjögren's syndrome) (Ambrosetti et al 2004, Ramos-Casals et al 2007, Sriskandarajah and Dearden 2016).

Most patients with extranodal MZL present with Ann Arbor stage IE disease (ie, extranodal disease limited to the site of origin) without bone marrow or peripheral lymph node involvement. The clinical findings and presenting symptoms of extranodal MZL are generally related to the primary location. The stomach is the most common site of localization, accounting for approximately one-third of cases of extranodal MZL (Zinzani 2012). Advanced disease at diagnosis is more common in patients with nongastric extranodal MZL, with nearly 50% of those with non-GI lymphoma presenting with disseminated disease compared with approximately 25% with gastric lymphoma (Troch et al 2011).

Patients with extranodal MZL have a favorable outcome with an average 5-year OS of more than 85% in most series. A study in an unselected population of patients with MZL subtypes included in the SEER database revealed a worse prognosis for patients with respiratory and GI lymphomas (5-year lymphoma-related death of 9.5%-14.3%) compared with those with disease at ocular adnexal and endocrine sites (4.5%-7.8%; $p < 0.0001$) (Olszewski and Castillo 2013).

1.1.2. Nodal MZL

Nodal MZL is a primary nodal lymphoma in the absence of previous or concurrent involvement of any extranodal site. It is rare, composing 10% of MZL cases and approximately 2% of all NHLs (Lymphoma Research Foundation 2017b). The diagnosis of nodal MZL is based on evaluation of nodal biopsy in the context of the clinical presentation. No specific diagnostic hallmarks of nodal MZL, including typical cytogenetic abnormalities, have been reported. Morphologically and according to immunophenotype, cases of nodal MZL can resemble either extranodal (MALT) MZL or splenic MZL.

Nodal MZLs appear as a heterogeneous disease with tumors hypothesized to originate from different subsets of marginal zone B cells, including virgin B cells expressing unmutated V_H genes, memory B cells showing somatic mutations, and germinal center B cells (Conconi et al 2001).

Most patients with nodal MZL present with disseminated peripheral and abdominal nodal involvement. Less than half of the patients present with bone marrow involvement, and peripheral blood involvement is quite rare (Armitage and Weisenburger 1998, Berger et al 2000, Non-Hodgkin's Lymphoma Classification Project 1997).

Patients with nodal MZL have an average 5-year OS of 60% to 70% and a 5-year event-free survival of approximately 30%.

1.1.3. Splenic MZL

Splenic MZL grows in a marginal zone pattern in the spleen; however, no clinical overlap occurs with extranodal and nodal MZLs and, as such, is clinically distinct. Splenic MZL constitutes

approximately 20% of all MZL cases and < 1% of all NHLs (Armitage and Weisenburger 1998, Lymphoma Research Organization 2017b).

Splenic MZL is hypothesized to arise from a post–germinal center memory B cell of splenic type (Swerdlow et al 2016). Although the precise molecular pathogenesis has not been clearly defined, acquired somatic mutations as seen with other cancers may play an important role. Overexpression of genes involved in B-cell receptor signaling, tumor necrosis signaling, and NF-κB activation have been observed and warrant more systemic studies of pathogenesis (Ruiz-Ballesteros et al 2005).

Similar to extranodal MZL, there is an association between splenic MZL and infection with viruses, such as HCV and Kaposi's sarcoma-associated herpes virus (Hermine et al 2002, Benavente et al 2011).

Patients with splenic MZL typically present with splenomegaly, lymphocytosis, and cytopenias primarily caused by hypersplenism and less frequently to autoantibodies or bone marrow infiltration. Unlike most other NHLs, lymphadenopathy and involvement of extralymphatic organs is rare (Franco et al 2003). Approximately 90% or more of cases are Stage IV disease at presentation.

The course of splenic MZL is generally extremely indolent, with a median OS > 10 years; however, a subset of cases characterized by a more aggressive disease course exhibited a median survival of 18 months (Chacón et al 2002).

1.2. Treatment for Marginal Zone Lymphoma

Treatment selection for patients with MZL depends on disease characteristics, including type, stage, and location as well as other patient characteristics, such as age and overall health. Because MZL is most often a slow-growing disease, a "watch-and-wait" approach is appropriate until symptoms appear.

H. pylori–positive gastric MALT lymphoma is initially treated with antibiotics in combination with proton pump inhibitors. In cases where gastric MALT lymphoma relapses or becomes refractory after antibiotic therapy, treatment options include rituximab (RITUXAN®) with or without chemotherapy, chlorambucil (or other alkylating agents), radiation therapy, and surgery.

In patients with symptomatic non-gastric MALT lymphoma, treatment may include surgery for certain sites (lung, breast) or radiation therapy, as needed. More advanced disease is usually initially treated with immunotherapy and chemotherapy, including bendamustine (TREANDA®) plus rituximab and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

When treatment is necessary in patients with symptomatic nodal MZL, options include radiation therapy, chemotherapy and/or immunotherapy, and other treatments commonly used in other types of slow-growing lymphomas, such as follicular lymphoma.

Some patients with splenic MZL may undergo a splenectomy. Patients ineligible for surgery may receive low-dose radiation of the spleen or rituximab with or without chemotherapy. In some cases, because of the association of this type of lymphoma with HCV, interferon with or without antiviral therapy may be given to patients who show evidence of HCV infection.

In January 2017, ibrutinib (IMBRUVICA®) was granted accelerated approval from the US FDA for use as treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti-CD20–based therapy (see Section 1.2.1; Imbruvica 2017).

Several other drugs and drug combinations are being studied in clinical trials of MZL and include chemotherapy agents (bendamustine), monoclonal antibodies (blinatumomab, obinutuzumab, pembrolizumab, and ibritumomab), antibody drug conjugate (brentuximab), small molecules (idelalisib, copanlisib, duvelisib, TGR-1202, and venetoclax), proteasome inhibitor (bortezomib), immunomodulators (lenalidomide and ublituximab), and radioimmunotherapy strategies (^{90}Y-ibritumomab tiuxetan).

1.2.1. Ibrutinib

Ibrutinib, a first-in-class, oral, once-daily therapy that inhibits BTK, was approved by the FDA as treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti-CD20–based therapy (Imbruvica 2017). The accelerated approval was based on data from a Phase 2, open-label, multi-center, single-arm study in subjects with MZL. The efficacy analysis included 63 subjects with extranodal (MALT; n = 32), nodal (n = 17), and splenic (n = 14) MZLs. The median time on study was 16.6 months, and the median duration of therapy was 11.7 months. Objective response rate was 46% (95% CI: 33.4%-59.1%) as assessed by an IRC using adopted International Working Group criteria for malignant lymphoma; 3.2% of subjects had a CR and 42.9% had a PR. The median time to response was 4.5 months (range: 2.3-16.4 months), and median DOR was not reached (range: 16.7 months to not reached). In the EU, ibrutinib has not yet received Committee on Human Medicinal Products approval for MZL.

The most common AEs (AEs ≥ 20%) of any grade included the following: fatigue (44%), diarrhea (43%), anemia (35%), nausea and thrombocytopenia (25% each), peripheral edema (24%), cough and arthralgia (22% each), and dyspnea and upper respiratory tract infection (21%). Adverse events ≥ Grade 3 occurred in 40 subjects (63%); most common events were anemia (14%), pneumonia (8%), and fatigue (6%). Serious AEs of any grade occurred in 28 subjects (44%), with Grade 3/4 pneumonia being the most common AE (5 subjects [8%]). Three TEAEs resulted in death due to disease progression, cerebral hemorrhage, and parainfluenza virus infection leading to multiple organ failure. The most common AE leading to treatment discontinuation was diarrhea in 2 subjects (3%).

1.3. INCB050465

Phosphatidylinositol 3-kinases belong to a family of lipid-signaling kinases that phosphorylate phosphoinositides of the inositol ring (Cantley 2002). Phosphatidylinositol 3kinases are divided into 3 classes (Class I, II, and III) according to their structure, regulation, and substrate specificity. Class I PI3Ks, which include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, are dual-specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate, giving rise to phosphatidylinositol-3,4,5-trisphosphate. Phosphatidylinositol-3,4,5-trisphosphate functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration. The recognition that aberrant signal transduction occurs in malignant B-lymphocytes via the PI3K pathways resulting in disease progression has led to a focus on agents that modulate these signaling pathways.

INCB050465 is a potent inhibitor of PI3Kδ (IC_{50} value = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members. INCB050465 does not significantly inhibit (< 30% inhibition) a broad panel of kinases when tested at a concentration of 100 nM (refer to the INCB050465 Investigator's Brochure [IB]). INCB050465 is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of human B-cell lines. This effect is not due to general cytotoxicity. Compared with inhibition of B-cell proliferation, INCB050465 is similarly potent in blocking helper T-cell differentiation but is > 100 times less potent in assays that measure effects on human T-cell and natural killer cell proliferation or monocyte function. These data suggest that the impact of INCB050465 on the human immune system will largely be restricted to B-cell and helper T-cell differentiation. The IC_{90} for pAKT inhibition of Pfeiffer cells in human whole blood is 77 nM. Preclinical toxicology studies supported evaluation of INCB050465 in human clinical studies (IB).

INCB050465 is being evaluated as a monotherapy in a Phase 1/2, dose-escalation and expansion study (INCB 50465-101, NCT02018861; Phillips et al 2016). As of 18 AUG 2017, data were available for 72 subjects who received INCB050465 administered orally at QD doses of 5 mg (n = 1), 10 mg (n = 3), 15 mg (n = 3), 20 mg (n = 34), 30 mg (n = 27), and 45 mg (n = 4). The median duration of treatment was 122.5 days (range: 7-690). Adverse events observed in ≥ 20% of subjects were nausea (36%), diarrhea (35%), fatigue and rash (each 31%), and cough and vomiting (each 24%). New or worsening ≥ Grade 3 anemia, thrombocytopenia, and neutropenia occurred in 7%, 10%, and 20% of subjects, respectively. No ≥ Grade 3 nonhematological treatment-related AEs were reported in ≥ 10% of subjects. Serious AEs that occurred in ≥ 2 subjects included diarrhea (n = 5); pyrexia (n = 4); colitis, sepsis, and hypotension (n = 3 each); and ventricular tachycardia, pneumonia, exfoliative dermatitis, respiratory failure, syncope, urinary tract infection, bronchitis, and bacteremia (n = 2 each). Fourteen (19%) of the 72 subjects discontinued study treatment due to the following 10 AEs: diarrhea (n = 3); exfoliative dermatitis and colitis (n = 2 each); and pneumonitis, rash, psoriasis, neutropenia, pleural effusion, cytomegalovirus colitis, and hypercalcemia (n = 1 each). No liver function test abnormalities > Grade 1 were reported while subjects were receiving study treatment. No dose-limiting toxicities were identified, and the maximum tolerated dose was not reached.

Pharmacokinetics analysis showed the t_{max} is 0.5 to 1 hour, the terminal half-life is approximately 8 to 12 hours, and exposure appeared to be dose-proportional between 5 mg QD and 45 mg QD at steady state. The pharmacodynamic analyses demonstrated robust and sustained pathway inhibition at all dose levels tested (Phillips et al 2016). Refer to the IB for further details (IB).

As of 18 AUG 2017, 30 objective responses as reported by investigators were observed in 55 evaluable subjects with DLBCL, follicular lymphoma, MZL, and mantle cell lymphoma. These results include 3 CMRs and 4 PRs (1 PR and 3 PMR) among 9 evaluable subjects with MZL. Six objective responses, including 2 CMRs, occurred by the time of the first disease assessment (9 weeks), and 1 CMR occurred around the 18-week disease assessment visit. Among the 7 objective responses, 2 demonstrated 100% reduction in their target lesions. The longest duration of study treatment among subjects with MZL was approximately 57 weeks; all subjects have discontinued treatment. Of note, none of the subjects with MZL had received prior treatment with a BTK inhibitor.

1.4. Study Rationale

Substantial progress has been made in defining the etiology and critical cellular and molecular pathological events of MZLs. However, given the rarity of the disease, there remains a lack of large databases or clinical data on this subset of patients. Therefore, the decision regarding treatment strategies is less well-defined, and a continued improvement in the clinical understanding of MZLs and development of specific therapies for MZL is warranted.

Study INCB 50465-204 was initially designed to enroll 2 cohorts, of which one would comprise subjects who had received prior treatment with ibrutinib. The BTK inhibitor, ibrutinib, is the first-ever approved treatment for patients in the United States with MZL who require systemic therapy and have received at least 1 prior anti-CD20–based therapy; approval was based on accelerated approval and a confirmatory trial is ongoing. Several observational studies have shown that patients with mantle cell lymphoma and chronic lymphocytic leukemia relapse after treatment with ibrutinib and that overall clinical outcome is poor (Cheah et al 2015, Stevens and Spurgeon 2015, Martin et al 2016). Martin et al (2016) revealed that 114 patients with available survival data had a median OS of 2.9 months after cessation of ibrutinib. Given the short survival reported after treatment with ibrutinib, developing treatment options in the post-ibrutinib setting is warranted. This population represents an unmet medical need. Given the limited availability of ibrutinib (approved for MZL in the United States only), only very few subjects are eligible for enrollment into the prior-ibrutinib cohort. At the time of Protocol Amendment (Version) 3, only 2 subjects have been enrolled into Cohort 1 (subjects previously treated with ibrutinib) since the start of the study in JUN 2017. Therefore, Cohort 1 was closed to further enrollment for feasibility reasons.

INCB050465 is a potent and selective PI3Kδ inhibitor and preliminary data has demonstrated rapid and deep objective responses in subjects with relapsed MZL who were naive to a BTK inhibitor (see Section 1.3). This study is designed to further evaluate the efficacy and safety of INCB050465 in subjects with MZL that has relapsed after or was refractory to prior systemic therapy.

All subjects will initially receive INCB050465 administered orally at a dose of 20 mg QD for 8 weeks. Based on an *ex vivo* whole blood assay, the 20 mg QD dose provides exposure ranging from approximately 2-fold above the IC_{90} at trough to 19-fold above the IC_{90} at peak. Data from SEP 2016 show that of the 11 NHL subjects administered 20 mg QD, 10 achieved an objective response at the time of first disease assessment (9 weeks). However, among all evaluable subjects with an objective response (n = 20), 7 (35%) discontinued study treatment due to an AE. Consequently, after receiving 20 mg QD of INCB050465 for 8 weeks, subjects will receive either 20 mg once weekly (referred to as Treatment A) or 2.5 mg QD of INCB050465 (referred to as Treatment B).

The 20 mg once-weekly regimen is proposed to maintain response while providing time off from pathway inhibition, which may reduce the frequency of AEs leading to study treatment withdrawal (see Section 1.3). Pharmacodynamic data from Study INCB 50465-101 showed that a single dose of 20 mg exhibited maximal inhibition of AKT in an *ex vivo* pharmacodynamic assay, and PK modeling suggests that 20 mg once weekly will 1) achieve maximal inhibition equivalent to approximately 10 × IC_{90}, 2) exceed the IC_{90} for approximately 36 hours, and 3) have minimal to no inhibition for approximately half the dosing interval. This

once-weekly regimen is similar to that of another PI3K inhibitor (copanlisib), which is administered intravenously on Days 1, 8, and 15 of a 28-day cycle and which achieved 7 objective responses in 9 subjects with NHL (Patnaik et al 2016). Among the 51 subjects who received copanlisib, 4 discontinued treatment due to an AE. There were 2 events of Grade 3 noninfectious pneumonitis, 1 event of Grade 3 diarrhea, and no events of colitis.

The 2.5 mg QD regimen is proposed to provide enough exposure (estimated to be approximately $1 \times IC_{90}$ at peak) to maintain PI3K pathway inhibition but reduce the frequency of AEs that lead to study treatment withdrawal. The continuous QD regimen has demonstrated prolonged responses in both aggressive and indolent NHL, and a continuous lower dose will be evaluated in this study. One subject with follicular lymphoma who received a 10 mg QD dose achieved a CMR and remained on study treatment for approximately 13 months before withdrawing due to an AE (Grade 2 psoriasis).

1.5. Potential Risks and Benefits of the Treatment Regimen

INCB050465 has effects on the immune system. Therefore, subjects in this study will be monitored closely for evidence of infections or new cancers, and study treatment administration will be discontinued if there is evidence of clinically significant infection or new cancer.

While PJP has not been reported with the use of INCB050465 either as monotherapy or in combination therapy, subjects who receive INCB050465 in this study will receive PJP prophylaxis. Subjects will be asked to report all sulfa drug allergies and those allergic to standard PJP prophylaxis with sulfonamide antibiotics will receive either inhaled pentamidine or atovaquone for PJP prophylaxis; these subjects will not be given dapsone.

As presented in Section 1.3, the most common AEs (≥ 20%) observed with INCB050465 monotherapy have been nausea, diarrhea, fatigue, cough, rash, and vomiting. Serious AEs (≥ 2 subjects) have included colitis, diarrhea, sepsis, hypotension, ventricular tachycardia, pyrexia, respiratory failure, pneumonia, bronchitis, exfoliative dermatitis, syncope, urinary tract infection, and bacteremia. Dose modification guidance and supportive care guidelines for diarrhea/colitis are implemented in this study.

Based on efficacy and safety data from the ongoing Study INCB 50465-101, which evaluated a continuous 20 mg QD dose regimen, the treatment regimen for Study INCB 50465-204 will be 20 mg QD for 8 weeks, followed by either 20 mg once weekly or 2.5 mg QD of INCB050465. As detailed in Section 1.3, these regimens are proposed to assess whether the frequency of AEs leading to treatment withdrawal will be reduced while maintaining PI3K pathway inhibition and maintenance of response.

INCB050465 is metabolized primarily by CYP3A4; therefore, use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of INCB050465 will be prohibited.

The effects of INCB050465 on fetal development has not been evaluated nor is it known whether INCB050465 passes into human breast milk; therefore, subjects who are pregnant or breastfeeding are excluded from participation in this study.

There are no preclinical data available to date on the potential phototoxicity of INCB050465. Therefore, subjects enrolled in this study taking INCB050465 will be instructed by the site staff

to take precaution to protect themselves from the sun/ultraviolet light. This includes wearing long sleeves, long trousers, hats, and sunglasses.

Preliminary data in study INCB 50465-101 demonstrated efficacy of INCB050465 monotherapy in which 7 of 9 (78%) evaluable subjects with MZL had an objective response. The longest duration on study treatment for these subjects was approximately 57 weeks.

2. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, [redacted] objectives and endpoints described herein are applicable for both cohorts (Table 1). See Section 9 for details on the analysis of endpoints for each cohort.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of INCB050465 in terms of ORR in subjects with MZL that is relapsed or refractory after at least 1 systemic treatment regimen.	ORR defined as the percentage of subjects 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 subjects who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess CRR.	CRR defined as the percentage of subjects 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.

Table 1: Study Objectives and Endpoints (Continued)

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Men and women, aged 18 or older (except in South Korea, aged 19 or older).
2. Histologically confirmed MZL, including extranodal, nodal, and splenic subtypes.
3. Previously received 1 or more lines of systemic therapy, including at least 1 anti-CD20 antibody (either as monotherapy or in combination as chemoimmunotherapy), with documented progression or documented failure to achieve CR or PR after the most recent systemic treatment regimen.
    a. Subjects in Cohort 1 must have received prior ibrutinib (**NOTE:** Cohort 1 will be closed to further enrollment with Protocol Amendment [Version] 3).
    b. Subjects in Cohort 2 must <u>not</u> have received a prior BTK inhibitor (eg, ibrutinib).
    c. Subjects with *H. pylori*-positive gastric extranodal MZL who received an initial treatment with currently accepted antibiotics may be considered eligible if, after antibiotic regimen, subject has histologically confirmed MZL and was subsequently treated with at least 1 line of systemic therapy.

4. Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the LDi and ≥ 1.0 cm in the longest perpendicular diameter as assessed by CT or MRI per response criteria for lymphomas (Cheson et al 2014).
    a. Subjects with splenic MZL who do not meet the radiographically measurable disease criteria described herein are eligible for participation provided that bone marrow infiltration of MZL is histologically confirmed.
5. Subjects must be willing to undergo an incisional or excisional lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue.
    a. Subjects with splenic MZL who do not have a tumor to biopsy or an archival tumor tissue sample are eligible for participation provided subject is willing to undergo a bone marrow biopsy or provide an archival bone marrow biopsy that was obtained since completion of last therapy and within 2 years before the date of the first dose of study treatment; bone marrow sample must show histologically confirmed infiltration of MZL.
6. Life expectancy > 3 months.
7. ECOG performance status 0 to 2 (Oken et al 1982; see Appendix B).
8. Adequate hematologic, hepatic, and renal function (values must not be achieved with growth factors):
    a. ANC ≥ 1.0×10^9/L.
    b. Hemoglobin ≥ 8.0 g/dL.
    c. Platelet count ≥ 50×10^9/L.
    d. Total bilirubin ≤ 1.5 × ULN. Subjects with documented history of Gilbert's syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
    e. ALT/AST ≤ 3.0 ULN or ≤ 5 × ULN in the presence of liver metastases.
    f. Calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault Equation (Cockcroft and Gault 1976) or the estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease formula.
9. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 45 years of age).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through at least 93 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Evidence of DLBCL transformation.
   a. Subjects with presumptive evidence of transformation based on clinical assessment of factors such as, but not limited to, increasing lactate dehydrogenase, rapidly worsening disease, or frequent B-symptoms, must be ruled out for a transformation to a more aggressive disease, such as DLBCL.
2. History of central nervous system lymphoma (either primary or metastatic) or leptomeningeal disease.
3. Prior treatment with idelalisib, other selective PI3Kδ inhibitors, or a pan-PI3K inhibitor.
4. Allogeneic stem cell transplant within the last 6 months, or autologous stem cell transplant within the last 3 months before the date of the first dose of study treatment.
5. Active graft versus host disease.
6. Use of immunosuppressive therapy within 28 days of the date of study treatment administration. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, tacrolimus, or high-dose corticosteroids. Subjects receiving corticosteroids must be at a dose level ≤ 10 mg/day within 7 days of the study treatment administration.
7. Receipt of anticancer medications or investigational drugs within the following intervals before the date of the first dose of study treatment:
   a. < 10 weeks from completion of any radio- or toxin-immunoconjugates.
   b. < 6 weeks for mitomycin-C or nitrosoureas.
   c. < 4 weeks for immunotherapy.
   d. < 3 weeks for radiotherapy.
   e. < 3 days for ibrutinib (**NOTE:** Cohort 1 [subjects who received prior ibrutinib] will be closed to further enrollment with Protocol Amendment [Version] 3).
   f. < 2 weeks for any investigational agent or other anticancer medications.
8. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
9. Prior treatment-related toxicities have not resolved to NCI CTCAE v4.03 (NCI 2010) ≤ Grade 1 before the date of the first dose of study treatment, except for stable chronic toxicities (≤ Grade 2) not expected to resolve (eg, stable Grade 2 peripheral neurotoxicity).

10. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
11. Use or expected use during the study of any prohibited medications, including potent CYP3A4 inhibitors or inducers (see Appendix D), within 14 days or 5 half-lives (whichever is longer) before the date of study treatment administration.
12. Significant concurrent, uncontrolled medical condition, including, but not limited to, renal, hepatic, hematological, GI, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
13. Current or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
14. History of stroke or intracranial hemorrhage within 6 months of the date of study treatment administration.
15. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment or exposure to a live vaccine within 30 days of dosing.
16. Known HIV infection or positivity on immunoassay. **Note:** HIV screening test is optional for subjects enrolled in the United States, but subjects with known HIV infection in the United States will be excluded.
17. Liver disease: HBV or HCV infection: Subjects positive for HBsAg or hepatitis B core antibody will be eligible if they are negative for HBV-DNA; these subjects should be considered for prophylactic antiviral therapy. Subjects positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
18. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and/or cardiac conduction issues within 6 months of the date of study treatment administration.
19. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
20. Presence of an abnormal ECG that is clinically meaningful. Screening QTc interval > 450 milliseconds is excluded (corrected by Fridericia). In the event that a single QTc is > 450 milliseconds, the subject may enroll if the average QTc for 3 ECGs is < 450 milliseconds.
21. Unable to swallow and retain oral medication, malabsorption syndrome, disease significantly affecting GI function, total resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
22. Known hypersensitivity or severe reaction to INCB050465 or its excipients (see IB).
23. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.

24. Currently pregnant or breastfeeding.
25. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
26. Inability to comprehend or unwilling to sign the ICF.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2, open-label study designed to evaluate the safety and efficacy of 2 INCB050465 treatment regimens in subjects diagnosed with relapsed or refractory MZL (see Figure 1). A total of approximately 90 subjects will be enrolled.

Subjects with MZL that is relapsed or refractory to at least 1 line of prior systemic therapy that included an anti-CD20 antibody will be screened for eligibility. The study was originally planned to enroll 2 cohorts:

- Cohort 1: Subjects who have received prior ibrutinib (n = 60)
- Cohort 2: Subjects who have not received a prior BTK inhibitor (n = 60)

However, given the limited availability of ibrutinib (approved for MZL in the United States only), the number of subjects with relapsed or refractory MZL previously treated with ibrutinib is low. At the time of Protocol Amendment (Version) 3, only 2 subjects have been enrolled into Cohort 1, 18 months after the study start in JUN 2017. Therefore, Cohort 1 was closed to further enrollment for feasibility reasons.

Subjects already enrolled into Cohort 1 will continue to receive study treatment per the Protocol, and their data will be reported and analyzed separately from subjects in Cohort 2.

The first 60 subjects in Cohort 2 and any subjects enrolled in Cohort 1 who meet the eligibility criteria will be further allocated to 1 of 2 study treatment regimens through the IWRS (see Section 5.1):

- Treatment A: INCB050465 20 mg QD PO for 8 weeks followed by 20 mg once weekly PO.
  - Subjects in Cohort 1 receiving Treatment A will be referred to as Cohort 1A.
  - Subjects in Cohort 2 receiving Treatment A will be referred to as Cohort 2A.
- Treatment B: INCB050465 20 mg QD PO for 8 weeks followed by 2.5 mg QD PO.
  - Subjects in Cohort 1 receiving Treatment B will be referred to as Cohort 1B.
  - Subjects in Cohort 2 receiving Treatment B will be referred to as Cohort 2B.

To better understand the safety and efficacy of INCB050465, an additional 30 subjects will be enrolled into one of the two treatment regimens (A or B) being evaluated in this Study. The treatment regimen will be selected after enrollment is completed for Cohort 2 (ie, 60 subjects enrolled) and after evaluation of emerging safety and efficacy data from this and other

monotherapy studies of INCB050465 in NHL. Once a treatment regimen is selected, the non-selected treatment regimen will be closed to further enrollment. Subjects receiving the non-selected treatment regimen may switch to the selected treatment regimen or remain on their current treatment regimen, provided the subject has not met study-treatment withdrawal criteria and there are no safety concerns for their current treatment regimen. There will be no re-baselining for subjects who switch treatment regimens and all subjects will continue to follow the same assessment schedule.

NOTE: The primary, secondary, [redacted] objectives and endpoints described in Section 2 are applicable for both cohorts; however, the cohorts will be analyzed separately, when applicable, as detailed in Section 9.

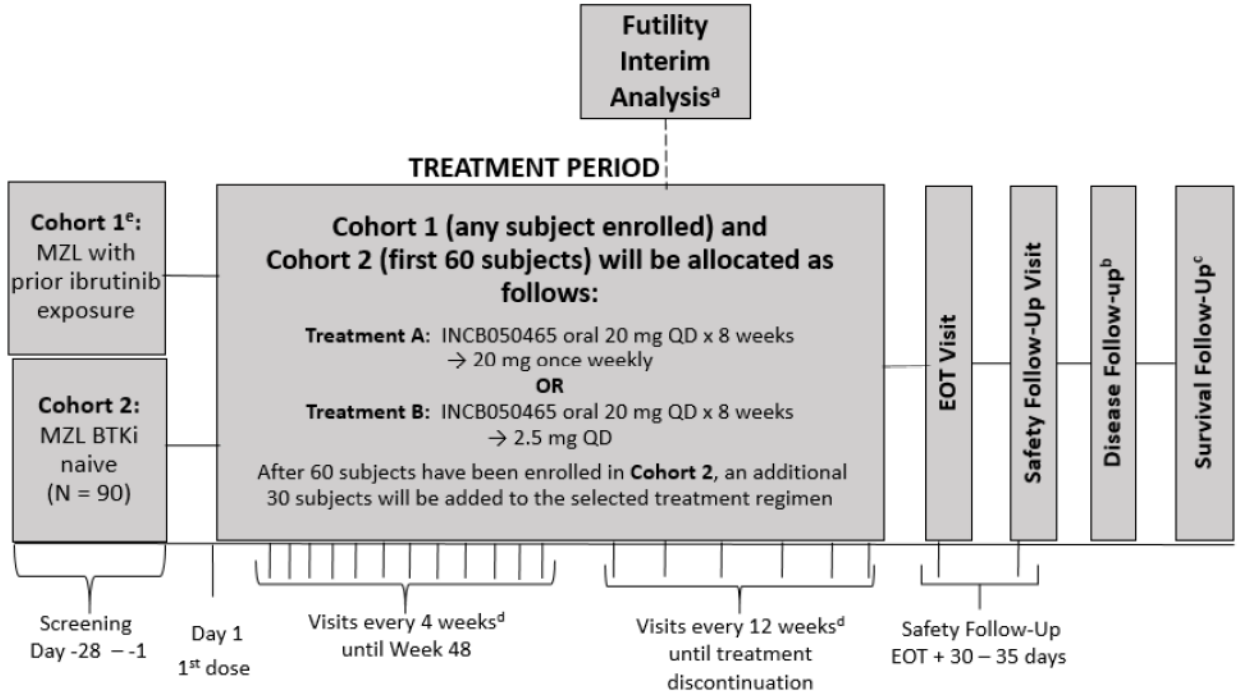
Subjects will receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

Subjects will be monitored for safety and efficacy periodically until disease progression, death, unacceptable toxicity, or withdrawal of informed consent. An IDMC will review safety data periodically as stated in the IDMC charter. Subjects will be evaluated for ORR by an IRC and followed for DOR, PFS, and OS.

An interim futility analysis is planned for Cohort 2 when 30 subjects 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 2 will be terminated for futility if $\leq$ 10 of the 30 subjects responded (ie, CR or PR) based on assessments provided by the IRC. A timely assessment of response will be performed to avoid the risk of overenrollment.

After treatment discontinuation, subjects will be followed for safety and survival. Subjects who have discontinued study treatment due to reasons other than disease progression will be followed for either radiologic disease progression, the start of a new anticancer therapy, or death, whichever comes first. It is expected that the final analysis will occur no later than 2 years after the first dose of INCB050465 is administered to the last subject treated.

Figure 1: Study Design of INCB 50465-204



BTKi = Bruton's tyrosine kinase inhibitor; EOT = end of treatment; MZL = marginal zone lymphoma; QD = once daily
[a] A futility analysis will be performed for Cohort 2 when the first 30 patients have been treated and evaluated for response (see Section 9.6).
[b] Subjects who discontinue study treatment for a reason other than disease progression will continue with disease assessments by radiologic imaging every 8, 12, or 24 weeks as appropriate with disease progression.
[c] Every 12 weeks by clinic visit, telephone, or e-mail.
[d] Urine pregnancy and dispensing of study treatment will occur every 4 weeks.
[e] Per Protocol Amendment Version 3, Cohort 1 is closed to further enrollment

4.2. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made. Safety will be objectively assessed using NCI CTCAE v4.03 (NCI 2010) guidelines and reviewed by the IDMC. Tumor response will be assessed by an IRC using the CT-based criteria of the Lugano classification (Cheson et al 2014).

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

The study will enroll approximately 90 subjects at approximately 100 global investigative sites.

4.3.2. Replacement of Subjects

No subjects will be replaced at any time during this study.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 28-day intervals. If the subject discontinues study treatment, the treatment period will end, and the subject will enter the 30 to 35-day safety follow-up period, after which the subject will enter the survival follow-up period (see Section 6.4.3). Subject participation is expected to average approximately 25 months.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when **all** subjects have discontinued from the study (see Section 5.7) **or** have completed at least 24 months of study participation (starting from the first dose of study treatment). It is estimated that the study will take approximately 2 years to accrue approximately 90 subjects and that the final analysis will be performed no later than 2 years after the first dose of study treatment is administered to the last subject treated. Subjects who are still on study treatment and who have no evidence of progressive disease at the end of the study will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits (see Section 5.8).

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the IDMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The IDMC will recommend termination of the study if warranted, as described in the IDMC Charter (see also Section 9.5).

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the IWRS in order to receive a subject number and treatment allocation.

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

Site staff will contact the IWRS to allocate the subject to treatment assignment and obtain the initial study treatment assignment. The investigator or designee will select the assigned bottles of study treatment from their stock that correspond to the number provided by the IWRS and dispense the study treatment to the subject. All subsequent dispensing of study treatment should follow this process. Refer to the IWRS Manual for detailed information.

If a subject is mistakenly given a bottle of study treatment that is not the bottle assigned by the IWRS, the IWRS help desk must be notified immediately. The reason for the misallocation of the study treatment must be documented by the study site and reported to the IRB/IEC.

For subjects who signed an ICF but are not allocated study treatment and for subjects who are allocated study treatment but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. INCB050465

5.2.1. Description and Administration

Details of INCB050465 are shown in Table 2.

Table 2: Description and Administration of INCB050465

Compound Name	INCB050465
Dose strengths	1 mg, 2.5 mg, 5 mg, and 20 mg
Form	Tablet
Active compound	INCB050465
Route of administration	Oral
Dose and regimen for Treatment A	20 mg QD for 8 weeks followed by 20 mg once weekly
Dose and regimen for Treatment B	20 mg QD for 8 weeks followed by 2.5 mg QD
Instructions	INCB050465 will be taken orally with water without regard to food [redacted] INCB050465 should be taken at approximately the same time each day.

For QD administration, if a dose is missed by more than 12 hours, then the subject should skip the dose and take the next scheduled dose at the usual time. For once-weekly dosing, if the dose is missed by more than 2 days, then the subject should skip the dose and take the next scheduled dose.

5.2.2. Supply, Packaging, and Labeling

INCB050465 will be provided as 1 mg, 2.5 mg, 5 mg, and 20 mg tablets packaged in high-density polyethylene bottles. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

Pneumocystis jirovecii pneumonia prophylaxis is required as coadministration with INCB050465. The prophylactic agents will be obtained from commercial supplies and will be reimbursed by Incyte. Investigators are responsible for ensuring that subjects receive commercially available supplies of the selected prophylactic agents as required per Protocol. The contents of the label will be in accordance with all applicable regulatory requirements. Further details are available in Section 5.6.1 and the Pharmacy Manual.

5.2.3. Storage

Bottles of INCB050465 should be stored at ambient conditions (15°C to 30°C or 59°F to 86°F).

5.2.4. Instruction to Subjects for Handling INCB050465

The subject must be instructed in the handling of INCB050465 as follows:

- To store study treatment at room temperature.
- To remove from the study treatment bottle only the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.

- To make every effort to take doses on schedule.
- To report any missed doses.
- To keep INCB050465 in a safe place and out of reach of children.
- To bring all used and unused study treatment kits to the site at each visit.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with study treatment will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study treatments with them to the study visits in order for site personnel to conduct tablet counts to assess study treatment accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.4. Treatment Interruptions and Adjustments

5.4.1. Criteria and Procedures for Dose Interruptions and Reductions of INCB050465

Treatment with INCB050465 may be interrupted for up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been interrupted for more than 14 days before restarting treatment with INCB050465.

5.4.1.1. Dose Modifications

Dose modification guidance for AEs that have been previously observed in subjects receiving INCB050465 or are potential class-effect AEs are provided (see Table 3 and Table 5). The starting dose and dose reduction levels of INCB050465 are provided (see Table 4). Individual decisions regarding dose interruption and reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study treatment and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose reduction guidelines.

Table 3: Guidelines for Interruption and Restarting INCB050465

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• Grade 3 AST and/or ALT (> 5.0 × ULN). **Note:** In subjects with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt INCB050465 and monitor weekly until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at next lower dose with medical monitor approval. Monitor as clinically indicated.
Hematology	
• Grade 3 ANC (< 1.0 × 10^9/L). • Grade 2 platelet count (50 to < 75 × 10^9/L) for subjects who enrolled with platelets > 100 × 10^9/L. • Grade 3 platelet count (< 50 × 10^9/L) for subjects who enrolled with platelets ≤ 100 × 10^9/L.	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. For Grade 3 ANC, monitor at least weekly. **Step 2:** Restart INCB050465 at same dose; monitor as clinically indicated.
• Grade 4 ANC (< 0.5 × 10^9/L). • Grade 3 or Grade 4 febrile neutropenia. • Platelet count is Grade 4 (< 25 × 10^9/L).	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved ≤ Grade 2. (Monitor at least weekly.) **Step 2:** Restart INCB050465 at same dose. Monitor as clinically indicated. If reoccurs, restart at next lower dose.
Other toxicities	
• Diarrhea/colitis.	See Table 5.
• Pneumonitis (Grade 1).	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
• Pneumonitis (Grade ≥ 2).	Permanently discontinue INCB050465.
• Skin toxicity (eg, rash, pruritus, unless otherwise specified; Grade 2 and 3).	**Step 1:** Interrupt INCB050465 until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose.
• Exfoliative dermatitis (Grade 1).	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
• Exfoliative dermatitis (≥ Grade 2).	Permanently discontinue INCB050465.
• Intestinal perforation (any grade).	Permanently discontinue INCB050465.
• PJP infection.	Interrupt INCB050465. Permanently discontinue INCB050465 if PJP infection is confirmed.
• CMV infection.	Subjects with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting INCB050465 for subjects with CMV viremia and clinical signs of infection until the infection has resolved. Restart INCB050465 reduced by 1 dose level if approved by the medical monitor.

Table 3: Guidelines for Interruption and Restarting INCB050465 (Continued)

ADVERSE EVENT	ACTION TAKEN
• Varicella zoster infection.	Interrupt INCB050465. Restart INCB050465 only by approval of the medical monitor.
• Any Grade 1 or Grade 2 toxicity unless otherwise specified.	Continue INCB050465 and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified.	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose. If interrupted for > 14 days, contact the medical monitor for approval to restart INCB050465. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue INCB050465 administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity.	Discontinue INCB050465 administration and follow-up per Protocol. Exceptions require approval of sponsor.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CMV = cytomegalovirus; IV = intravenous; ULN = upper limit of normal.

Table 4: Dose Levels and Reductions for INCB050465

Timepoint	Treatment A	Treatment B
Starting dose	20 mg QD for 8 weeks (Day 1 through Day 56)	20 mg QD for 8 weeks (Day 1 through Day 56)
First dose reduction	10 mg QD	10 mg QD
Second dose reduction	5 mg QD	5 mg QD
Week 9 (Day 57) onward	20 mg once weekly[a]	2.5 mg QD[b]
First dose reduction	10 mg once weekly	1 mg QD[c]
Second dose reduction	5 mg once weekly	NA

[a] All subjects will receive 20 mg once weekly at Week 9 (Day 57) regardless of prior dose level, unless a dose modification of a switch to a QW schedule before Week 9 is required for diarrhea/colitis management (see Table 5).
[b] All subjects will receive 2.5 mg QD at Week 9 (Day 57) regardless of prior dose level, unless a dose modification of a switch to a QW schedule is required for diarrhea/colitis management (see Table 5).
[c] Further dose modification due to diarrhea or colitis for subjects on 1 mg QD is permitted (see Table 5).

5.4.2. Supportive Care Guidelines for Diarrhea/Colitis

Subjects should be informed to immediately report to the investigator any event of diarrhea. Treatment with INCB050465 may be interrupted or modified according to the guidelines in Table 5 to allow for resolution of diarrhea/colitis.

Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. For any ≥ Grade 1 diarrhea, subjects should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Subjects should try to eat 5 to 6 small meals per day; low-fat,

high-protein foods; and cooked instead of raw vegetables. Subjects may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements and may also try crackers, gelatin, noodles, or oatmeal. Subjects should avoid fried, fatty, greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements (Coutré et al 2015).

For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection (including CMV), which might require additional supportive care.

It may be necessary to perform conditional procedures such as colonoscopy with biopsy as part of evaluation of the event. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain or cramping, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

Table 5: Guidelines for Dose Modification of INCB050465 for Diarrhea/Colitis

ADVERSE EVENT	ACTION TAKEN
• Diarrhea (Grade 1).	**Step 1:** Treat with antimotility agents (eg, 4 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care (see Section 5.4.2). Monitor approximately every 48 hours until resolved. If not improved after 48 hours, treat per guidance for Grade 2.
• Diarrhea (Grade 2).	**Step 1:** Interrupt INCB050465. Perform work-up for infection (including CMV, *C. difficile*, etc) immediately. Initiate or continue supportive care (see Section 5.4.2). Monitor approximately every 48 hours until resolution. **Step 2:** If improved within 48 hours and/or infection* is confirmed, restart INCB050465 at the **same schedule and dose** after resolved to ≤ Grade 1 and continue to monitor. *For infectious diarrhea/colitis, follow institutional standard-of-care guidelines and restart INCB050465 according to clinical judgement after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** If not improved within 48 hours and infection is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. **Step 4:** When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea is ≤ Grade 1, restart INCB050465 at the next lower dose with approval of the medical monitor (see Table 4 for dose levels). **Step 5:** If Grade 2 diarrhea reoccurs, treat per guidance for diarrhea (≥ Grade 3)/noninfectious colitis. **Step 6:** If ≥ Grade 2 diarrhea reoccurs a third time, permanently discontinue INCB050465.

Table 5: Guidelines for Dose Modification of INCB050465 for Diarrhea/Colitis (Continued)

<table>
<tr><th>ADVERSE EVENT</th><th>ACTION TAKEN</th></tr>
<tr><td>• Diarrhea (≥ Grade 3).
• Noninfectious colitis (any grade; confirmed or suspected).</td><td>Step 1: Interrupt INCB050465. Perform work-up for infection (including CMV, C. difficile, etc) immediately. Initiate or continue supportive care (see Section 5.4.2). Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms[a] suggestive of colitis. Monitor every 48 hours until resolution.
Step 2: If infection* is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids.
*For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgement after resolved to ≤ Grade 1. Consult with medical monitor if needed.
Step 3: When diarrhea/colitis resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea/colitis is ≤ Grade 1, restart INCB050465 as described herein and with approval of the medical monitor. Continue to monitor.
<table>
<tr><th>INCB050465 Current Dose</th><th>Dose Modification</th></tr>
<tr><td>Any dose with QD dosing</td><td>20 mg QW regardless of Treatment A or B assignment</td></tr>
<tr><td>20 or 10 mg QW</td><td>Restart next lower dose</td></tr>
<tr><td>5 mg QW</td><td>Permanently discontinue</td></tr>
</table>
Step 4: If ≥ Grade 3 diarrhea/colitis (any grade) reoccurs, permanently discontinue INCB050465.</td></tr>
</table>

[a] Diarrhea accompanied by abdominal pain and/or mucus or blood in stool.

5.4.3. Supportive Care Guidelines for Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia appear to be PI3Kδ class-effect toxicities. Investigators should ensure that subjects understand the need to seek medical care when they have conditions that could become life-threatening in the presence of cytopenias (eg, neutropenic fever or bleeding with low platelets). Subjects should be instructed to report immediately any signs of infection, unexpected bleeding, or sudden, extremely painful headaches.

5.4.4. Definition for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as an AE consistent with an immune phenomenon associated with study treatment exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with INCB050465. Special attention should be paid to AEs that may be suggestive of potential irAEs. Based on emerging data from the ongoing Study INCB 50465-101, most irAEs occur after the first 9 weeks of study treatment administration. However, an irAE could occur at any time. Suspected irAEs should be discussed with the medical monitor when possible.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 3 and Section 5.4.1. For each

AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

5.5. Study Treatment Discontinuation

The decision to discontinue study treatment will not constitute study completion. In the event that study treatment is discontinued, the treatment period will be considered complete, and the follow-up periods will begin.

5.5.1. Criteria for Study Treatment Discontinuation

Subjects **must** be withdrawn from study treatment for any 1 of following reasons:

- The subject has experienced an unacceptable toxicity defined as follows:
  - Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
  - Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- The subject is unable to tolerate study treatment.
- The subject has an objective radiographic tumor response of PD.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.
- Informed consent is withdrawn.
  Note: Consent withdrawn means that the subject can no longer be followed. Subjects may choose to discontinue study treatment and remain in the study to be followed for disease progression and survival per the schedule of assessments.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be discontinued from study treatment in the following situations:

- If a subject is noncompliant with study procedures or study treatment administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.5.2. Procedures for Study Treatment Discontinuation

Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6.4. The last date of the last dose of study treatment and the reason for subject withdrawal will be recorded in the eCRF.

If a subject permanently discontinues study treatment, then the following should occur:

- The reason(s) for discontinuation must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
  - If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data will be entered in the EOT visit in the eCRF.
- The date of the EOT visit should be recorded in the IWRS.
- Subjects must be followed for safety for no less than 30 days after the EOT visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data will be collected. However, subjects may withdraw consent for study treatment but continue to be assessed for disease progression and survival per the schedule of assessments.

5.6. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before the date of study treatment administration (Day 1) will be recorded in the eCRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

5.6.1. *Pneumocystis Jirovecii* Pneumonia Prophylaxis

All subjects are required to receive a standard PJP prophylaxis regimen determined by the investigator (see Section 5.2.2). Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (NCCN 2017). Due to reports of cross-sensitivity between sulfonamides and dapsone, all subjects who have a known or suspected allergy to sulfonamides must receive either inhaled pentamidine or atovaquone for PJP prophylaxis. Prophylaxis should be given while subjects are receiving study treatment and should continue for at least 2 to 6 months after the last dose of study treatment.

5.6.2. Restricted Medications

- Use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through EOT.
- Short courses of systemic corticosteroid doses > 10 mg/day prednisolone or equivalent are permitted only in the case of severe or life-threatening complications, which cannot be controlled with other drugs, but are otherwise discouraged from the screening visit through EOT.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (see Appendix D) is discouraged, and investigators should seek other options where possible.

- Use of P-glycoprotein substrates of clinical relevance should be used with caution (ie, aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan) from the screening visit through the EOT visit.
- Localized radiotherapy will be permitted if administered as treatment for pain or impending compression fractures and with prior approval of the medical monitor.

5.6.3. Prohibited Medications

- Use of potent inducers and inhibitors of CYP3A4 is prohibited (see Appendix D). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Apart from the study treatments, the use of any anticancer medications as described (see Section 3.2) through the 30-day follow-up is prohibited.
- Exposure to a live vaccine within 30 days of study treatment through 3 months after the last dose of INCB050465.

5.7. Criteria for Study Discontinuation

A subject will be discontinued from the study for any 1 of the following reasons:

- The subject has died.
- The subject is considered lost-to-follow-up when he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site (eg, after 3 telephone calls and/or a certified letter or local equivalent).
- Informed consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB or IEC.

5.8. Treatment After the End of the Study

At the end of the study as defined in Section 6.5, subjects who have completed at least 24 months of study participation (starting from the first dose of study treatment), who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 6), and all laboratory assessments will be performed as indicated in Table 7. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. By convention, Week 4, Week 8, Week 12, etc, means the completion of 4, 8, or 12 weeks, respectively. Table 8 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule of assessments. See Section 7 for instructions on each assessment.

Table 6: Schedule of Assessments

Procedure	Section	Screening	Treatment			EOT	Follow-Up		
							Safety	Disease	Survival
		Days -28 to -1	Day 1[a]	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)		EOT + 30-35 Days		Every 12 Weeks (± 1 Week)
Informed consent	7.1	X							
Contact IWRS	7.2	X	X	X	X	X			
Inclusion and exclusion criteria	3	X	X						
Demography and medical history	7.3	X							
[redacted]									
Prior/concomitant medications	7.4	X	X	X	X	X	X		
AE assessment[d]	8.1	X	X	X	X	X	X		
Comprehensive physical exam	7.5.2	X[e]				X			
Disease-specific physical exam	7.5.3		X	X	X		X		
Vital signs	7.5.4	X	X	X	X	X	X		
12-lead ECG	7.5.5	X	X[f]	X[f]	X	X	X		
ECOG performance status	7.5.6	X	X	X	X	X	X		
CT/MRI scan	7.6.1	X		Every 8 weeks through Week 24 (± 1 week), then every 12 weeks through Week 96, and then every 24 weeks thereafter until PD				X[c]	
Bone marrow exam	7.6.2	X[g]		X[h]				X[h]	
Prophylactic treatment for PJP	5.6.1		X[i]						
Study treatment dispensing	5.1.1		X	X	X				
Study treatment compliance	5.3		X	X	X	X			
INCB050465 administration	5.2.1		X	X	X				
Disease follow-up	6.4.2							X[c]	
Survival follow-up	6.4.3								X[j]

[a] All procedures are to be performed before administration of study treatment on Day 1.

[redacted]

[d] Adverse events will be monitored from the time the subject signs the ICF until at least 30 days after the last dose of study treatment. Serious AEs occurring more than 30 days after the last dose of study treatment should be reported to the sponsor or its designee if the investigator suspects a causal relationship to the study treatment. Once detected, AEs should be followed until resolved or judged to be permanent.

[e] Height required at screening only.

[f] Timed triplicate ECGs will be obtained during the Day 1 visit (predose) and Week 4 visit (predose and 1.5 hours [± 15 minutes] after receiving study treatment).

[g] Required at baseline except for reasons provided in Section 7.6.2.

[h] If disease is present in bone marrow at baseline, a bone marrow biopsy will be required to confirm CR or may be performed as clinically indicated. For subjects with splenic MZL without measurable disease (ie, only have histologically confirmed bone marrow infiltration), a bone marrow biopsy/examination must be performed when the number of lymphocytes in the blood normalize.

[i] *Pneumocystis jirovecii* pneumonia prophylaxis should be given while subjects are receiving study treatment and continue for at least 2 to 6 months after the last dose of study treatment.

[j] May be conducted by clinic visit, telephone, or email.

Table 7: Schedule of Laboratory Assessments

Laboratory Tests[a]	Section	Screening	Treatment				EOT	Safety Follow-Up
		Day -28 to -1	Day 1[b]	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)	Other		EOT + 30-35 Days
Serum chemistries	7.5.7.1	X	X[c]	X	X		X	X
Hematology[d]	7.5.7.1	X	X[c]	X	X	X[e]	X	X
Serology	7.5.7.3	X		X[f]	X[f]			
HIV testing	7.5.7.3.1	X[g]						
Serum pregnancy	7.5.7.2	X[h]					X	
Urine pregnancy	7.5.7.2					X[i]		
[redacted]								
Tumor/bone marrow biopsy	7.8.5	X[m]				X[n]		

[a] All laboratory assessments must be performed at a central laboratory, unless otherwise specified (see Section 7.5.7).
[b] All laboratory assessments are to be performed before administration of study treatment on Day 1, unless otherwise specified.
[c] If chemistry and/or hematology laboratory assessments occurred in the preceding 7 days, Day 1 assessments may be omitted.
[d] Hematology will be collected every 2 weeks for the first 8 weeks.
[e] Week 2 (Day 15) and Week 6 (Day 43) ± 3 days.
[f] Samples for CMV DNA analysis only.
[g] Optional for subjects enrolled in the United States.
[h] Only for females of childbearing potential; negative serum pregnancy test must be obtained within 14 days before administration of study treatment. Screening test may be performed centrally or at the investigative site laboratory.
[i] Only for females of childbearing potential; if a urine pregnancy test is positive, then a serum pregnancy test should be performed. Urine pregnancy must be collected every 4 weeks until last dose of study treatment.
[redacted]

Table 8: Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Serology
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen C-reactive protein Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is > ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count (absolute) Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA CMV DNA HIV antibody (immunoassay)[a] **Pregnancy Testing** Only for female subjects of childbearing potential Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] Optional for subjects enrolled in the United States.

6.1. Screening

Screening is the interval between signing the ICF and the date of first dose of study treatment (Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. Central laboratory results for serum chemistry, hematology, and serology will be used to determine eligibility. Serum pregnancy tests may be performed centrally or at the investigative site laboratory.

Procedures conducted as part of the subject's routine clinical management (eg, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes, provided that the procedure meets the Protocol-defined criteria and has been performed in the screening interval. All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed by the investigator to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine subject eligibility. Additionally, a subject who fails screening may repeat the screening process 1 time if the

investigator believes there has been a change in eligibility status (eg, after recovery from an infection). Such subjects will be assigned a new subject ID number.

6.2. Treatment

The treatment period begins on the date of first dose of study treatment (Day 1). Day 1 must be no more than 28 days after the subject has signed the ICF. Dates for subsequent study visits will be determined based on this date and should occur within the visit windows outlined in the schedule of assessments (see Table 6) unless delayed for safety reasons. At Day 1, results from screening visit evaluations should be reviewed by the investigator to determine whether the subject continues to meet the eligibility requirements, as specified in the Protocol. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

6.3. End of Treatment

There is no defined date of EOT. When the subject permanently discontinues study treatment, then the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study treatment, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.

If a subject is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, then the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will continue to be followed for disease assessments by radiologic imaging per the schedule of

assessments (see Table 6). Every effort should be made to collect information regarding disease status until 1 of the following occurs:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study treatment, confirmed disease progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period and should be followed up every 12 weeks by a clinic visit, telephone, or e-mail. The site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF.

For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. End of Study

The end of the study will be when **all** subjects have met any of the study discontinuation criteria in Section 5.7 **or** have completed at least 24 months of study participation (starting from first dose of INCB050465).

At the end of the study, subjects who have completed at least 24 months of study participation, who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

6.6. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion and appropriate clinical and laboratory measurements performed based on AEs or other findings.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Web Response Technology Procedure

The IWRS will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IWRS will be contacted to obtain the treatment assignment. Additionally, the IWRS will be contacted at each regular study visit to update the study treatment supply (see Section 5.1.1 and Table 6).

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history, including date of diagnosis of MZL, histology, current staging, grade, sites of disease, prior antineoplastic therapy, surgery, radiation, and other details related to the disease under study, will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All prior and concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before enrollment and up to the end of study treatment will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general,

nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Comprehensive Physical Examination

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

The comprehensive physical examination will include height (at screening only), body weight (within 1 lb or 0.5 kg), and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination (eg, reflexes, strength, Romberg's test, vibration sense, and gross sensory perception).

7.5.3. Disease-Specific Physical Examination

A disease-specific physical examination will be a symptom-directed evaluation and will include assessment(s) of the body systems or organs, as indicated by subject disease and symptoms, AEs, or other findings as determined by the investigator or designee. A disease-specific physical examination must include a measurement of the subject's body weight (within 1 lb or 0.5 kg), and an evaluation of any AEs or symptoms that the subject has previously reported.

7.5.4. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.5. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECGs will be performed locally and be interpreted by the investigator at the site and used for immediate subject management. Baseline ECGs obtained during screening can be performed using a single measurement; however, ECGs may be performed in triplicate if the single QTc measurement is > 450 milliseconds (corrected by Fridericia; see Section 3.2). The decision to include or exclude a subject or discontinue a subject's participation in the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. If a single measurement demonstrates a QTc interval > 500 milliseconds, 2 more ECGs should be obtained over a brief period, and the averaged QTc intervals should be used to determine whether the study treatment should be interrupted (see Section 5.4.1).

7.5.5.1. Timed Electrocardiograms

Timed triplicate ECGs will be obtained during the Day 1 visit (predose) and at Week 4 (predose and 1.5 hours [± 15 minutes] after receiving study treatment). When triplicate ECGs are being obtained, individual measurements should be performed 5 minutes (± 3 minutes) apart.

7.5.6. ECOG Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; see Appendix B) will be assessed. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

7.5.7. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in the schedule of laboratory assessments (see Table 7). Specific laboratory assessments are provided in Table 8.

All laboratory assessments, including those conducted during unscheduled visits, will be performed at a central laboratory, with the exception of the following, in which case the investigative site laboratory or an accredited local laboratory may be used:

- Serum pregnancy testing performed at screening (see Section 7.5.7.2)

  Note: A local laboratory assessment (including reference ranges) will be recorded into the subject's eCRF only if there is no accompanying central laboratory assessment and the local laboratory assessment caused a change in subject management (eg, a dose interruption or reduction) or was an AE or SAE.

7.5.7.1. Chemistry and Hematology

All chemistry and hematology assessments (see Table 7 and Table 8) will be performed from blood samples collected using institutional best practices.

7.5.7.2. Pregnancy Testing

A serum pregnancy test at screening will be required for all women of childbearing potential (see Section 3.1) as shown (Table 7) and can be performed either at the central or local laboratory.

Urine pregnancy tests will be conducted as shown (Table 7). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a positive urine test, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study treatment and continue participation in the study.

7.5.7.3. Serology

Serology assessments will be performed at a central laboratory (see Table 7 and Table 8).

7.5.7.3.1. HIV Testing

Subjects enrolled outside of the United States must have an HIV immunoassay test at screening to ensure negative HIV status (see Section 3.2). HIV testing is optional for subjects enrolled in the United States.

7.6. Efficacy Assessments

7.6.1. Computed Tomography Scan or Magnetic Resonance Imaging

All subjects will undergo a diagnostic-quality CT or MRI at screening to evaluate for the presence of measurable disease. Assessments will be performed on the neck, chest, abdomen, and pelvis, and will include evaluation of the spleen for size and presence of splenic nodules. During the screening period, if CT/MRI assessment was performed as standard of care before signing of the ICF but within 28 days of Day 1, then the results from that assessment may be recorded in the eCRF if used in lieu of a study-specific assessment.

Subjects with a spleen size > 13 cm and/or splenic nodules at screening will continue to follow the disease assessment schedule for radiologic imaging. If subjects without splenomegaly at screening develop splenomegaly (ie, palpable spleen) during study treatment, then radiologic imaging should be performed. The disease assessment schedule also applies to those subjects who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Radiologic imaging should not be delayed for interruption of study treatment.

7.6.2. Bone Marrow Examination

Bone marrow examination is required as a baseline assessment at screening except in the following circumstances:

- Subject had a bone marrow examination performed as per standard of care within approximately 60 days of the first dose of study treatment.
- Subject had a bone marrow examination performed after the last treatment for NHL and the results showed lymphoma involvement of the bone marrow.

Subsequently, a bone marrow examination will be performed and sample(s) will be sent to a local histopathology laboratory to confirm CR on imaging or as clinically indicated. [redacted] 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. Sample collection and processing instructions will be provided in the Laboratory Manual.

Note: For subjects with splenic MZL without measurable disease (ie, only have histologically confirmed bone marrow infiltration), a bone marrow biopsy must be performed when the number of lymphocytes in the blood normalize.

All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible.

The pathology report result from the bone marrow examination will be captured in the eCRF.
Note: Bone marrow biopsies and aspirates collected at screening should be evaluated locally. These materials are not to be sent to the central laboratory or the sponsor.

[redacted]

7.6.4. Independent Review Committee

All radiologic imaging (CT or MRI) will be submitted to the central radiology vendor for review. 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; see Appendix C) by independent reviewers as described in the Imaging Charter.

[redacted]

[redacted]

7.8.5. Tumor or Bone Marrow

Subjects must have an available archival tumor biopsy sample (preferably obtained since completion of last therapy) or be willing to undergo a pretreatment tumor biopsy at baseline. Subjects with splenic MZL unable to provide a tumor biopsy sample must have an archival bone marrow biopsy that was obtained since completion of last therapy and within 2 years before the date of the first dose of study treatment or be willing to undergo a bone marrow biopsy at

baseline. Tumor tissue may be obtained on study for purposes of analyzing safety, efficacy, [redacted]

[redacted]

7.9. Other Study Procedures

7.9.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit.

The subject reminder card will indicate the date/time of the next visit and will also remind the subjects of which days they should not take their morning dose before coming to the clinic (see Section 7.7). The reminder cards for the Week 4 visit will have an area on which the date and time of the last dose taken (from the previous day) and the time of their last meal before the visit should be recorded.

7.9.2. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will collect data as described (see Section 6.4.3).

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (e.g., hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study treatment Adverse events (including laboratory abnormalities that constitute AEs) should be described using a

diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5 (NCI 2010). If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death due to AE

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (e.g., not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or non-drug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (e.g., between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (e.g., "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition

- An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
- A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
- Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.

- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study treatment, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study treatment should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous

SAE Report Form, such as the outcome of the event (e.g., resolved or ongoing), treatment provided, action taken with study drug because of the SAE (e.g., dose reduced, interrupted, or discontinued), or subject disposition (e.g., continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented of the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Adverse Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities.

- ALT $\geq 5 \times$ ULN
- AST $\geq 5 \times$ ULN
- Colitis
- Diarrhea $\geq$ Grade 2
- Intestinal perforation
- Rash $\geq$ Grade 2
- Exfoliative dermatitis
- Pneumonitis
- PJP infection
- CMV infection
- Herpes simplex virus infection
- Varicella zoster virus infection

8.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a

pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.7. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of INs. Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.8. Independent Data Monitoring Committee

An IDMC will be formed and will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the IDMC are addressed in the approved IDMC charter.

8.9. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of INCB050465. The full analysis set will be used for the summary of demographics, baseline characteristics, subject disposition, and analyses of all efficacy data.

The safety population includes the same set of subjects as the full analysis set. This population will be used for all safety analyses.

[redacted]

9.2. Selection of Sample Size

Cohort 1: Will be closed to further enrollment with Protocol Amendment (Version) 3.

Cohort 2: Up to 90 subjects will be enrolled. If the true ORR is 60%, then there is approximately 90% or 96% probability of observing the lower bound of the 95% CI of ORR $\geq$ 40% with 60 or 90 subjects, respectively.

9.3. Level of Significance

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

9.4. Statistical Analyses

All analyses will be conducted independently for Cohort 1 and Cohort 2, and there will not be multiplicity adjustment between the cohorts.

Within each of the 2 cohorts, efficacy data from the 2 treatment regimens (A and B) will be combined for the purpose of the primary and secondary efficacy analyses. Safety data will be summarized by treatment regimen and combined.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

Objective response rate is defined as the percentage of subjects with a CR or PR as determined by revised response criteria for lymphomas (Cheson et al 2014).

The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated. This is considered the primary efficacy analysis for each of the 2 cohorts.

The ORR as reported by the investigator and its 95% exact binomial CIs will also be calculated.

Response data will be analyzed when all subjects in the full analysis set of the respective cohort have reached at least 1 postbaseline disease assessment or have progressed, withdrawn from the study, or died.

9.4.1.2. Secondary Efficacy Analyses

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 subjects who achieve an overall response (ie, CR or PR) as determined by revised response criteria for lymphomas (Cheson et al 2014). For subjects who have not progressed and are still alive at the time of the analysis, DOR will be censored on the day of last evaluable disease assessment. For subjects who have discontinued study or have started other anticancer treatment, DOR will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anticancer treatment.

Progression-free survival is defined as the time from the date of 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 subjects who have not progressed and are still alive at the time of the analysis, PFS will be censored on the day of last evaluable disease assessment. For subjects who have discontinued study or have started other anticancer treatment, PFS will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anticancer treatment. For subjects who have no baseline or no postbaseline disease assessment, PFS will be censored with censored duration of 1 day.

The Kaplan-Meier estimation of median DOR and PFS as determined by the IRC and its 95% CIs will be provided.

Complete response rate is defined as the percentage of subjects with a CR as determined by revised response criteria for lymphomas (Cheson et al 2014).

The CRR as determined by the IRC and its 95% exact binomial CIs will be calculated.

Overall survival is defined as the time from the date of first dose of study drug to death due to any cause. For subjects who are still alive at the time of the analysis, OS will be censored on the date the subjects is last known to be alive. The Kaplan-Meier estimation of median OS and its 95% CIs will be provided.

Target lesion size is measured by the sum of the product of diameters of all target lesion sizes. Best percentage change in target lesion size from baseline will be summarized descriptively.

9.4.1.3. Other Efficacy Analyses

Analyses of ORR, DOR, CRR, and PFS as reported by the investigator will be summarized as described above.

Analyses of ORR, DOR, CRR, PFS as determined by IRC, and OS will also be summarized by treatment regimens (A or B) within each cohort.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

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. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship 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 treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

Number (%) of subjects reporting any TEAEs, any SAEs, any Grade 3 or 4 TEAEs, any treatment-related TEAEs, any treatment-related SAEs, any treatment-related Grade 3 or 4 TEAEs, any fatal TEAE, and any TEAEs leading to treatment interruption/dose reduction/discontinuation will be summarized and tabulated by system organ class and preferred term.

9.4.2.2. Clinical Laboratory Tests

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03 when applicable. The following summaries will be produced for the laboratory data:

- Descriptive statistics of the value and change from baseline at each assessment time will be provided.
- For laboratory parameters that have CTC grading, shift tables will be provided showing change in CTC grade from baseline to the worst grade postbaseline.
- For laboratory parameters where CTC grades are not defined, shift tables from baseline to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits when necessary.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 10), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 10: Criteria for Clinically Notable Vital Sign Abnormalities

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

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 11). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 11: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.2.5. Adverse Events of Special Interest

Adverse events of special interest (see Section 8.5) will be summarized as detailed in the Statistical Analysis Plan.

[redacted]

[redacted]

9.5. Analyses for the Data Monitoring Committee

Preplanned analyses of safety will be provided to the IDMC as specified in the IDMC charter. In addition, the IDMC will make recommendations to the sponsor at the planned interim futility analyses (see Section 9.6). The process by which the IDMC will make recommendations and decisions will be documented in the IDMC Charter.

9.6. Interim Analysis

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

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.

- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.
- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made

available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use, and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Subject names will not be supplied to the sponsor or its designee. Only the subject number will be recorded in the eCRF; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results

are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

For Male Subjects Participating in the Study

In addition to the aforementioned contraceptive methods, male subjects must also use a condom during intercourse from the time of first dose of study treatment and through at least 93 days after last dose of study treatment. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCORES

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX C. LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT (CT-BASED ONLY)

Site	CT-Based Response
	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Nonmeasured lesion	Absent
Organ enlargement	Regress to normal
New lesions	None
Bone marrow	Normal by morphology; if indeterminate, IHC negative
	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default • When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm but smaller than normal, use actual measurement
Nonmeasured lesions	Absent/regressed, but no increase
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal
New lesions	None
Bone marrow	Not applicable
	Stable disease
Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Nonmeasured lesions	No increase consistent with progression
Organ enlargement	No increase consistent with progression
New lesions	None
Bone marrow	Not applicable

Site	CT-Based Response
	Progressive disease (requires at least 1 of the following)
Individual target nodes/nodal lesions	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm – Increase by ≥ 50% from PPD nadir – Increase in LDi or SDi from nadir: o 0.5 cm for lesions ≤ 2 cm o 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly • New or clear progression of pre-existing nonmeasured lesions • Regrowth of any previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma • New or recurrent involvement of the bone marrow

5PS = 5-point scale; LDi = longest transverse diameter of lesion; PPD = cross-product of the longest transverse diameter and perpendicular diameter; SDi = shortest axis perpendicular to the longest transverse diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Note: aPET 5-point scale: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX D. CYP3A INHIBITORS AND INDUCERS

CYP3A inhibitors or inducers may alter INCB050465 concentration. These include, but are not limited, to the drugs listed below.

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
indinavir /RIT	Protease Inhibitors
tipranavir/RIT	Protease Inhibitors
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
indinavir	Protease Inhibitors
troleandomycin	Antibiotics
telaprevir	Antivirals
danoprevir / RIT	Antivirals
elvitegravir / RIT	Treatments of AIDS
saquinavir / RIT	Protease Inhibitors
lopinavir / RIT	Protease Inhibitors
itraconazole	Antifungals
voriconazole	Antifungals
mibefradil	Calcium Channel Blockers
LCL161	Cancer Treatments
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice DS	Food Products
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors
boceprevir	Antivirals
Moderate CYP3A Inhibitors	
erythromycin	Antibiotics
fluconazole	Antifungals
atazanavir / RIT	Protease Inhibitors

darunavir	Protease Inhibitors
diltiazem	Calcium Channel Blockers
darunavir / RIT	Protease Inhibitors
dronedarone	Antiarrhythmics
crizotinib	Kinase Inhibitors
atazanavir	Protease Inhibitors
letermovir	Antivirals
GSK2647544	Alzheimer's Disease & Dementia Treatments
aprepitant	Antiemetics
casopitant	Antiemetics
amprenavir	Protease Inhibitors
faldaprevir	Antivirals
imatinib	Antineoplastic Agents
verapamil	Calcium Channel Blockers
netupitant	Antiemetics
nilotinib	Kinase Inhibitors
grapefruit juice	Food Products
tofisopam	Benzodiazepines
cyclosporine	Immunosuppressants
ACT-178882	Renin Inhibitors
ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal Medications
isavuconazole	Antifungals
cimetidine	H-2 Receptor Antagonists
FK1706	Central Nervous System Agents
Weak CYP3A Inhibitors	
tabimorelin	Hormone Replacement
amlodipine	Calcium Channel Blockers
ranolazine	Cardiovascular Drugs
breviscapine	Herbal Medications
lomitapide	Other Antilipemics
fosaprepitant (IV)	Antiemetics
Seville orange (Citrus aurantium) juice	Food Products
amiodarone	Antiarrhythmics
diosmin	Herbal Medications
chlorzoxazone	Muscle Relaxants
M100240	Antihypertensive Agents
fluvoxamine	Antidepressants
ranitidine	H-2 Receptor Antagonists

goldenseal	Herbal Medications
clotrimazole	Antifungals
tacrolimus	Immunosuppressants
palbociclib	Kinase Inhibitors
cilostazol	Antiplatelets
ticagrelor	Antiplatelets
peppermint oil	Food Products
ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase Inhibitors
Guan Mai Ning	Herbal Medications
osilodrostat	Adrenal Steroidogenesis Inhibitors
AZD2327	Depression Treatments
piperine	Food Products
resveratrol	Food Products
roxithromycin	Antibiotics
suvorexant	Hypnotics - Sedatives
propiverine	Anticholinergics
isoniazid	Antibiotics
berberine	Herbal Medications
oral contraceptives	Oral contraceptives
delavirdine	NNRTIs
daclatasvir	Antivirals
simeprevir	Protease Inhibitors
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
tolvaptan	Vasopressin Antagonists
almorexant	Hypnotics - Sedatives
GSK1292263	Other Antilipemics
evacetrapid	CETP inhibitors
linagliptin	Dipeptidyl Peptidase 4 Inhibitors
grazoprevir *(ingredient of Zepatier)*	Antivirals
lacidipine	Calcium Channel Blockers
cranberry juice	Food Products
pazopanib	Kinase Inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food Products
flibanserin	Central Nervous System Agents
lapatinib	Kinase Inhibitors
brodalumab	Immunomodulators Biologics

AMD070	Fusion Inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal Medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin Receptor Antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous Agents
ginkgo	Herbal Medications
teriflunomide	Other Immunomodulators

CYP3A Inducers

Inducers	Therapeutic class
Potent Inducers	
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's Wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
rifabutin	Antibiotics
phenobarbital	Anticonvulsants
Moderate Inducers	
ritonavir and St. Johns wort	None
semagacestat	Alzheimer's Treatments
efavirenz	NNRTIs
tipranavir and ritonavir	Protease Inhibitors
dabrafenib	Kinase Inhibitors
lesinurad	Antigout and Uricosuric Agents
bosentan	Endothelin Receptor Antagonists
genistein	Food Products
thioridazine	Antipsychotics
nafcillin	Antibiotics
talviraline	NNRTIs
lopinavir	Protease Inhibitors

modafinil	Psychostimulants
PF-06282999	Myeloperoxidase Inactivators
etravirine	NNRTIs
lersivirine	NNRTIs
telotristat ethyl	Antidiarrheals
Weak Inducers	
eslicarbazepine	Anticonvulsants
telaprevir	Antivirals
daclatasvir and asunaprevir and beclabuvir	Antivirals
amenamevir	Antivirals
garlic	Food Products
bexarotene	Other Antineoplastics
sarilumab	Immunomodulators Biologics
artesunate and mefloquine	Antimalarials
amprenavir (fosamprenavir)	Protease Inhibitors
raltegravir	HIV-Integrase Strand Transfer Inhibitors
vemurafenib	Kinase Inhibitors
troglitazone	Thiazolidinediones
dicloxacillin	Antibiotics
sorafenib	Kinase Inhibitors
rufinamide	Anticonvulsants
sirukumab	Immunomodulators Biologics
pleconaril	Antivirals
ginseng	Herbal Medications
boceprevir	Antivirals
sulfinpyrazone	Antigout and Uricosuric Agents
ginkgo	Herbal Medications
vinblastine	Vinca Alkaloids
nevirapine	NNRTIs
armodafinil (R-modafinil)	Psychostimulants
ticagrelor	Anticoagulants and Antiplatelets
LCL161	Cancer Treatments
vicriviroc and ritonavir	Treatments of AIDS
ritonavir	Protease Inhibitors
prednisone	Corticosteroids
oxcarbazepine	Anticonvulsants
danshen	Herbal Medications
clobazam	Benzodiazepines
echinacea	Herbal Medications

ticlopidine	Anticoagulants and Antiplatelets
isavuconazole	Antifungals
brivaracetam	Anticonvulsants
Stribild	Treatments of AIDS
pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
dexamethasone	Corticosteroids
terbinafine	Antifungals
quercetin	Food Products
glycyrrhizin	Herbal Medications
aprepitant	Neurokinin-1 Receptor Antagonists
pretomanib (PA-824)	Antibiotics
safinamide	MAO-B Inhibitors
oritavancin	Antibiotics
AZD 7325	Anxiolytics
methylprednisolone	Corticosteroids
topiramate	Anticonvulsants

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Administrative Change 1:	16 AUG 2017
Administrative Change 2 (Version 0-UK):	26 SEP 2017
Amendment (Version) 1:	24 JAN 2018
Amendment (Version) 1-FRA:	23 FEB 2018
Amendment (Version) 2-FRA:	28 MAR 2018
Amendment (Version) 2:	18 JUL 2018
Amendment (Version) 3:	07 DEC 2018
Amendment (Version) 4:	23 DEC 2019

Amendment 4 (23 DEC 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide additional guidance on dose modification in the event of diarrhea and colitis and to define the end of the study, including the option to receive continued treatment with INCB050465 in a rollover protocol.

1. **Section 5.4.1.1, Dose Modifications (Table 3: Guidelines for Interruption and Restarting INCB050465; Table 4: Dose Levels and Reductions for INCB050465); Section 5.4.2, Supportive Care Guidelines for Diarrhea/Colitis (Table 5: Guidelines for Dose Modification of INCB0050465 for Diarrhea/Colitis)**

   Description of change: Revision to text pertaining to interruptions and restarting INCB050465 for adverse events of diarrhea and colitis.

   Rationale for change: To provide additional dose modifications of INCB050465 for diarrhea and colitis.

2. **Synopsis; Section 4.5, Overall Study Duration; Section 5.8, Treatment After the End of the Study; Section 6.5, End of Study**

   Description of change: Text and new section added to describe that subjects who are receiving active study treatment and have no evidence of progressive disease at the end of the study will have the option to continue on INCB050465 provided within a rollover Protocol.

   Rational for change: To clarify what treatment options are available at the end of the study.

3. **Synopsis (Estimated Duration of Participation); Section 4.4, Duration of Treatment and Subject Participation; Section 4.5, Overall Study Duration; Section 5.7, Criteria for Study Discontinuation; Section 6.5, End of Study**

   Description of change: Text and new section added to define the following: a) criteria for a subject to be discontinued from the study and b) the end of study.

   Rational for change: To clarify when a subject will be discontinued from the study and when the study will end.

4. **Section 6, Study Assessments (Table 6: Schedule of Assessments)**

   Description of change: Changed frequency of study treatment dispensation and assessment of compliance from every 4 weeks to every 12 weeks starting at Week 48.

   Rationale for change: To align with the frequency of clinic visits after Week 48 whereby reducing the burden of extra clinic visits for the subjects.

5. **Section 9.1, Study Populations**

   Description of change: Removed the PP population.

   Rationale for change: For a single-arm, open-label study, the determination of subjects 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.

6. **Section 9.1, Study Populations; Section 9.4.1.1, Primary Efficacy Analysis**

   Description of change: The efficacy evaluable analysis set was replaced with the full analysis set.

   Rationale for change: To include all treated subjects in the efficacy analyses.

7. **Section 9.4.2.4, Electrocardiograms (Table 11: Criteria for Clinically Notable Electrocardiogram Abnormalities)**

   Description of change: Changed high threshold of QTcF interval from > 460 msec to > 450 msec for analysis purposes.

   Rationale for change: 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.

8. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

This amendment also incorporates the following from Protocol Administrative Change 2 dated 23 MAY 2019:

[redacted]

Amendment 3 (07 DEC 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to close enrollment in Cohort 1 and to increase the number of subjects enrolled in Cohort 2 to better understand the safety and efficacy of INCB050465 administered at one of the 2 treatment regimens.

1. **Synopsis; Section 1.2.1, Ibrutinib; Section 1.4, Study Rationale; Section 3.1, Subject Inclusion Criteria; Section 3.2, Subject Exclusion Criteria; Section 4.1, Overall Study Design (Figure 1, Study Design of INCB 50465-204); Section 4.3.1, Planned Number of Subjects; Section 4.5, Overall Study Duration; Section 9.2, Selection of Sample Size; Section 9.4.1.1, Primary Efficacy Analyses; Section 9.6, Interim Analysis**

   Description of change: Text has been added to describe the following: a) Cohort 1 will be closed to further enrollment, b) an additional 30 subjects will be enrolled into Cohort 2 and receive the selected treatment regimen, and c) subjects may switch over to the selected treatment regimen.

   Rationale for change: Due to the limited availability of ibrutinib (approved in the United States only) and the subsequent low number of subjects enrolled to date, enrollment into Cohort 1 will be closed. Additional subjects will be enrolled in Cohort 2 to better understand the safety and efficacy of INCB050465 administered at the selected treatment regimen. To allow all subjects to receive the selected treatment regimen, subjects initially allocated to the non-selected treatment regimen may switch over to the selected treatment regimen.

2. **Section 9.1, Study Populations**

   Description of change: Defined the efficacy evaluable analysis set that will be used for the efficacy analyses in place of the full analysis set.

   Rationale for change: The efficacy evaluable analysis set was added to clarify the population that will be included in the efficacy analyses.

3. **Section 10.4, Data Privacy and Confidentiality of Study Records**

   Description of change: Revision to language pertaining to the protection of personal data.

   Rationale for change: To comply with the General Data Protection Regulation 2016/679.

4. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications; Appendix D, CYP3A Inhibitors and Inducers**

   Description of change: Added tables of CYP3A inhibitors and inducers in Appendix D. These tables were updated and modified compared with the previous versions, which had been removed from Protocol Version 2 and placed in the Pharmacy Manual.

   Rationale for change: These tables were returned to the Protocol by the request of the German Regulatory Authority, BfArM.

5. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (18 JUL 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to modify the dose reduction schedules.

1. **Section 3.1, Subject Inclusion Criteria**

   Description of change: Criterion 8d was revised to allow subjects whose total bilirubin values are > 1.5 × ULN to enroll if the elevation is due to Gilbert's syndrome.

   Rationale for change: Gilbert's syndrome is a hereditary condition characterized by intermittent, unconjugated hyperbilirubinemia in the absence of hepatocellular damage and hemolysis. Consistent with other PI3Kδ inhibitors, elevated bilirubin due to Gilbert's syndrome is not expected to alter the risk/benefit profile for subjects taking INCB050465.

2. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications; Appendix B, Cytochrome P450 3A Inhibitors and Inducers**

   Description of change: Deleted appendix and corresponding cross-references.

   Rationale for change: Moved information to the Pharmacy Manual.

3. **Section 5.4, Treatment Interruption and Adjustments (Table 3: Guidelines for Interruption and Restarting INCB050465)**

   Description of change: Redefined "Grade 3 or Grade 4 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection" as Grade 3 or Grade 4 febrile neutropenia. Allowance is made to restart INCB050465 at the same dose after Grade 4 ANC, Grade 4 platelet count, or Grade 3 or Grade 4 febrile neutropenia resolve to ≤ Grade 2, rather than Grade 1, regardless of attribution.

   Rationale for change: A restart at the same dose level regardless of attribution is allowed to provide investigators flexibility in subject management. Study drug administration is allowed to begin at ≤ Grade 2 to be consistent with eligibility criteria, which start at Grade 2 for neutrophil and platelet counts.

4. **Section 5.4, Treatment Interruptions and Adjustments (Table 4: Dose Levels for INCB050465)**

   Description of change: Modified the dose reduction schedules.

   Rationale for change: The new schedules are being implemented to ensure that all subjects will remain on a QD dosing schedule for the first 8 weeks (Days 1-56) and to provide consistency between Treatments A and B.

5. **Section 6, Study Assessments (Table 6: Schedule of Laboratory Assessments, footnote a); Section 7.5.7, Laboratory Assessments**

   Description of change: Clarified the scenarios in which a local laboratory assessment may be performed and in which cases local laboratory values would be entered into the eCRF.

   Rationale for change: Clarification.

6. **Section 7.6.1, Computed Tomography Scan or Magnetic Resonance Imaging**

   Description of change: Clarified that spleen size and presence of splenic nodules should be assessed in all subjects at screening and subjects with enlarged spleen will continue to have radiologic imaging according to the Protocol schedule. Clarified that if an enlarged spleen is suspected at any time during the study, then radiologic imaging should be performed.

   Rationale for change: Clarification.

7. **Section 7.6.2, Bone Marrow Examination**

   Description of change: Clarified that bone marrow collected at screening (baseline) and after screening (postbaseline) should be sent to a local histopathology laboratory. [redacted]

   Rationale for change: Clarification.

8. **Appendix C, Lugano Classification for Response Assessment (CT-Based Only)**

   Description of change: PET-based response criteria were removed.

   Rationale for change: This study does not use PET scans to evaluate response.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2-FRA (28 MAR 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise the exclusion criterion for liver disease and incorporate other revisions requested by health authorities in order to align with global Protocol Amendment 1.

1. **Section 5.4.3, Supportive Care Guidelines for Neutropenia and Thrombocytopenia**

   Description of change: Provided instructions to investigators to remind subject to report signs or symptoms of infection, bleeding, or sudden, extremely painful headaches.

   Rationale for change: Requested by the US FDA.

2. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Criterion 17 was revised to allow for subjects who are positive for HBsAg or hepatitis B core antibody to enroll if they are negative for HBV-DNA and to remove risk of reactivation as exclusionary.

   Rationale for change: As there have been no reported HBV or HCV reactivations in INCB 50465-101, the exclusion criterion was amended to align with those of approved PI3K inhibitors.

3. **Section 1.3, INCB050465; Section 1.5, Potential Risks and Benefits of the Treatment Regimen**

   Description of change: Updated safety and efficacy data from Phase 1/2 study INCB 50465-101.

   Reason for change: Requested by German regulatory authority.

4. **Section 5.2.2, Supply, Packaging, and Labeling**

   Description of change: Clarified language on how PJP prophylactic agents will be supplied.

   Rationale for change: Incyte will not provide PJP prophylactic agents, but rather sites will be responsible for sourcing from commercial supply and Incyte will reimburse.

5. **Section 5.5.1, Criteria for Study Treatment Discontinuation**

   Description of change: The following bullet has been deleted from Section 5.5.1: If a subject is found not to have met eligibility criteria, then the medical monitor and investigator will collaborate to determine whether the subject should be withdrawn from the study.

   Rationale for change: Requested by US and Canadian regulatory authorities during review of other Incyte protocols.

6. **Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications**

   Description of change: Radiation therapy was removed from Section 5.6.3 as it was redundant with Section 3.2 (Exclusion Criterion 10), which lists excluded, concurrent anticancer therapies. A description of permitted radiotherapy was added to Section 5.6.2.

   Rationale for change: Administration of localized radiotherapy in cases of pain or impending compression fractures may be permitted to allow subjects who are otherwise benefitting to continue study treatment.

7. **Section 5.6.3, Prohibited Medications**

   Description of change: A statement was added noting that exposure to a live vaccine is prohibited within 30 days of study treatment through 3 months after the last dose of INCB050465.

   Rationale for change: Requested by MHRA.

[redacted]

9. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 6, Study Assessment (Table 5, Schedule of Assessments); Section 7.8.5, Tumor**

   Description of change: Language was added to allow subjects with splenic MZL to participate if a bone marrow biopsy is provided at baseline.

   Rationale for change: Subjects with splenic MZL may not have a tumor lesion to biopsy or an archival tumor tissue to provide. Therefore, a bone marrow sample histologically confirming infiltration of MZL is allowed.

10. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Provided information for male contraception methods.

    Rationale for change: Informational.

[redacted]

12. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1-FRA (23 FEB 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to institute hematology testing every 2 weeks for the first 8 weeks of INCB050465 dosing.

1. **Synopsis; Section 6, Study Assessments (Table 6, Schedule of Laboratory Assessments**

   Description of change: Study visits were added at Week 2 and Week 6 for hematology testing.

Rationale for change: Requested by the French National Agency for Medicines and Health Products Safety.

Amendment 1 (24 JAN 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to institute hematology testing every 2 weeks for the first 8 weeks of dosing and revise the exclusion criterion for liver disease.

The changes incorporated in the INCB 50465-204 Protocol Amendment 1 (Version 1 dated 24 JAN 2018) are summarized below.

1. **Synopsis; Section 6, Study Assessments (Table 6, Schedule of Assessments)**

   Description of change: Study visits were added at Week 2 and Week 6 for hematology testing.

   Rationale for change: Requested by the US FDA.

2. **Section 5.4.3, Supportive Care Guidelines for Neutropenia and Thrombocytopenia**

   Description of change: Provided instructions to investigators to remind subject to report signs or symptoms of infection, bleeding, or sudden, extremely painful headaches.

   Rationale for change: Requested by the US FDA.

3. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Criterion 17 was revised to allow for subjects who are positive for HBsAg or hepatitis B core antibody to enroll if they are negative for HBV-DNA and to remove risk of reactivation as exclusionary.

   Rationale for change: As there have been no reported HBV or HCV reactivations in INCB 50465-101, the exclusion criterion was amended to align with those of approved PI3K inhibitors.

4. **Section 1.3, INCB050465; Section 1.5, Potential Risks and Benefits of the Treatment Regimen**

   Description of change: Updated safety and efficacy data from Phase 1/2 study INCB 50465-101.

   Reason for change: Requested by German regulatory authority.

5. **Section 5.2.2, Supply, Packaging, and Labeling**

   Description of change: Clarified language on how PJP prophylactic agents will be supplied.

   Rationale for change: Incyte will not provide PJP prophylactic agents, but rather sites will be responsible for sourcing from commercial supply and Incyte will reimburse.

6. **Section 5.5.1, Criteria for Study Treatment Discontinuation**

   Description of change: The following bullet has been deleted from Section 5.5.1: If a subject is found not to have met eligibility criteria, then the medical monitor and investigator will collaborate to determine whether the subject should be withdrawn from the study.

   Rationale for change: Requested by US and Canadian regulatory authorities during review of other Incyte protocols.

7. **Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications**

   Description of change: Radiation therapy was removed from Section 5.6.3 as it was redundant with Section 3.2 (Exclusion Criterion 10), which lists excluded, concurrent anticancer therapies. A description of permitted radiotherapy was added to Section 5.6.2.

   Rationale for change: Administration of localized radiotherapy in cases of pain or impending compression fractures may be permitted to allow subjects who are otherwise benefitting to continue study treatment.

[redacted]

9. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 6, Study Assessment (Table 5, Schedule of Assessments); Section 7.8.5, Tumor**

   Description of change: Language was added to allow subjects with splenic MZL to participate if a bone marrow biopsy is provided at baseline.

   Rationale for change: Subjects with splenic MZL may not have a tumor lesion to biopsy or an archival tumor tissue to provide. Therefore, a bone marrow sample histologically confirming infiltration of MZL is allowed.

10. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Provided information for male contraception methods.

    Rationale for change: Informational.

[redacted]

12. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Administrative Change 2 (26 SEP 2017)

Overall Rationale for the Administrative Change:

The primary purpose of this administrative change is to address changes requested by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom.

The changes to the Protocol INCB 50465-204 Version 0 (22 MAR 2017) are summarized below.

1. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: A statement was added noting that male subjects participating in the study must also use a condom during intercourse from the time of first dose of study treatment and through at least 93 days after last dose of study treatment.

   Rationale for change: Requested by MHRA.

2. **Section 5.6.3, Prohibited Medications**

   Description of change: A statement was added noting that exposure to a live vaccine is prohibited within 30 days of study treatment through 3 months after the last dose of INCB050465.

   Rationale for change: Requested by MHRA.

3. **Appendix F, Protocol Amendment Summary of Changes**

   Description of change: This appendix was added to provide a description of the administrative changes to the Protocol to date and the rationale for changes.

   Rationale for change: To ensure compliance with Incyte's new standard Protocol template.

4. **Title Page; header of all pages in the Protocol; Page 2, Investigator Agreement**

   Description of change: Revised version number (Version 0-UK).

   Rationale for change: To denote the administrative changes made to this Protocol apply to all participating investigative sites in the United Kingdom.

Administrative Change 1 (16 AUG 2017)

Overall Rationale for the Administrative Change:

The primary purpose of this administrative change is to denote a version number associated with the protocol in response to a request from the National Research Ethics Service (NRES) in the United Kingdom.

This amendment includes the changes to the Protocol INCB 50465-204 (22 MAR 2017) summarized below.

1. **Cover Page and header of all pages in the Protocol**

   Description of change: The table on the cover page and header were revised to add a version number. This original protocol will be Version 0.