CLINICAL PROTOCOL

Protocol Number 101-09

A Phase 2 Study to Assess the Efficacy and Safety of Idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents

Version 9.0
Release Date: 05 September 2017

Gilead Sciences, Inc.
199 East Blaine Street
Seattle, WA 98102, USA

PROTOCOL IDENTIFIERS AND SPONSOR STUDY PERSONNEL

Project Code	Idelalisib
Therapeutic Area	Oncology
Study Sponsor Substance Identifier	Idelalisib (CAL-101/GS-1101)
IND Number **EudraCT Number**	101,254 2010-022155-33
Included in clinical trials.gov Database	Yes
Protocol Number	101-09
Protocol Version 9.0 Date	05 September 2017
Protocol Phase	Phase 2
Protocol Title	A Phase 2 Study to Assess the Efficacy and Safety of idelalisib in Subjects with Indolent B-Cell Non-Hodgkin Lymphomas Refractory to Rituximab and Alkylating Agents
Study Sponsor Medical Monitor	PPD Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102, USA Telephone: PPD Facsimile: PPD E-mail: PPD
Study Sponsor Clinical Program Manager	PPD Gilead Sciences, Inc. 199 East Blaine Street Seattle, WA 98102, USA Telephone: PPD Facsimile: PPD E-mail: PPD

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

By signing this document, the principal investigator confirms – on behalf of the investigator's institution – that the study will be conducted in accordance with the protocol; generally accepted standards of Good Clinical Practice (GCP); and all applicable laws, rules, and regulations relating to the conduct of the clinical study.

Principal Investigator Signature **Date**

Institution

SPONSOR PROTOCOL APPROVAL SIGNATURES

By signing this document, the sponsor's representatives confirm that this study will be conducted in compliance with the protocol; accepted standards of GCP; and all applicable laws, rules, and regulations relating to the conduct of the study. They also attest that data will be generated, documented, and reported consistent with the protocol; GCP; and relevant laws, rules, and regulations.

PPD

PPD
Associate Director, Clinical Research, Oncology
Gilead Sciences, Inc.

27 Sept 2017
Date

PPD

Clinical Program Manager
Gilead Sciences, Inc.

27 Sep 2017
Date

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS AND IDENTIFICATION OF TERMS

β-HCG	Beta human chorionic gonadotropin
ABCG2	Adenosine triphosphate-binding cassette sub-family G member 2 (see also BCRP)
ALL	Acute lymphocytic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AKT	AKT (a serine/threonine protein kinase)
AUC	Area under the concentration-time curve
ATC	Anatomical-Therapeutic-Chemical (drug coding system)
BAFF	B-cell activating factor belonging to the tumor necrosis factor family
BCR	B-cell receptor
BCRP	Breast cancer resistance protein (see also ABCG2)
BFU-e	Erythroid blast-forming units
BID	Twice per day
BTK	Bruton tyrosine kinase
CAL-101	Former product code name for GS-1101 and idelalisib
CD40	Antigen expressed on the surface of immune cells
CD-ROM	Compact disc read-only memory
CRF	Case report form
CFR	United States Code of Federal Regulations
CCL	Chemokine (C-C motif) ligand
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLL	Chronic lymphocytic leukemia
cGMP	Current Good Manufacturing Practices
CK	Creatine kinase
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CVP	Cyclophosphamide, vincristine, and prednisone
CXCL	Chemokine (C-X-C motif) ligand

CXCR	Chemokine (C-X-C motif) receptor
CYP	Cytochrome P450 enzyme
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
DNP-KLH	Dinitrophenol-keyhole limpet hemocyanin
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FACT-Lym	Functional Assessment of Cancer Therapy: Lymphoma
FDA	United States Food and Drug Administration
FDAMA	Food and Drug Modernization Act
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practices
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GS-1101	Gilead product code for idelalisib
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
IC_{50}	Concentration inducing 50% inhibition
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
Ig	Immunoglobulin
IND	Investigational New Drug (application)
iNHL	Indolent non-Hodgkin lymphoma
INR	International normalized ratio
ITT	Intention to treat
IRB/IEC	Institutional review board/independent ethics committee
IRC	Independent review committee
IWRS	Interactive web response system
K_2-EDTA	Potassium-ethylenediaminetetraacetic acid

LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LPL	Lymphoplasmacytoid lymphoma
MAA	Marketing Authorization Application
MTD	Maximum tolerated dose
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MZL	Marginal zone lymphoma
NDA	New drug application
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OAT	Organic anion transporter
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PIP3	Phosphatidylinositiol (3,4,5)-trisphosphate
PET	Positron-emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PI3Kδ	Phosphatidylinositol 3-kinase p110δ isoform
PJP	Pneumocystis jirovecii pneumonia (PJP)
PR	Partial response
PRO	Subject-reported outcome
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog (tumor suppressor)
PVA	Polyvinyl alcohol
QD	Once per day
QTcB	Cardiac QT interval corrected for heart rate by the method of Bazett
QTcF	Cardiac QT interval corrected by for heart rate by the method of Fridericia
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RNA	Ribonucleic acid
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisone
SSAD	Study sponsor awareness day

SSC	Study steering committee
SHIP	Inositol polyphosphate 5-phosphatase
SD	Stable disease
SLL	Small lymphocytic lymphoma
SPD	Sum of the product of the diameters (of nodal or tumor masses)
SPEP	Serum protein electrophoresis
$t_{1/2}$	Half-life
T_{max}	Time of maximum concentration
TTF	Time to treatment failure
TTR	Time to response
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WM	Waldenström macroglobulinemia

1. OVERVIEW

1.1. Background

Non-Hodgkin lymphomas (NHL) comprise the most common hematological malignancies. Among the variants of these cancers are indolent NHL (iNHL) subtypes that are slowly progressive over time. These disorders are characterized by lymphadenopathy that is frequently disturbing for subjects and can sometimes induce life-threatening organ dysfunction. Subjects may have B symptoms (fevers, night sweats, and/or weight loss) and fatigue. The goal of therapy is to induce tumor regression and delay tumor progression in order to control disease-related complications. Subjects are given sequential treatments with chemotherapeutic and immunotherapeutic agents to ameliorate bothersome adenopathy and symptoms. Despite use of agents with differing mechanisms of action, progressive resistance to treatment develops. New therapies with novel mechanisms of action are needed to offer additional treatment options for subjects with iNHL who are experiencing symptoms due to disease progression.

Phosphatidylinositol 3-kinases (PI3K) are a family of enzymes that are involved in proliferation, migration, and survival for many cell types. Among several isoforms of the enzyme is phosphatidylinositol 3-kinase p110δ (PI3Kδ), which is expressed in B-lymphocytes. Gilead Sciences, Inc., a pharmaceutical company located in Seattle, WA, has developed novel drugs that can suppress tumor growth by selectively inhibiting PI3Kδ activity. These efforts led to identification of idelalisib (GS-1101; formerly known as CAL-101), a 415-Dalton, orally bioavailable, new chemical entity with potential clinical utility in the treatment of cancers. In vitro studies in cultured lymphoma cells demonstrate that idelalisib abrogates PI3Kδ signaling and impairs malignant B-cell survival.

Nonclinical safety testing has supported clinical development of idelalisib. Safety pharmacology studies show no adverse effects on cardiopulmonary and neurological functioning. Toxicology studies in rats and dogs through 13 weeks indicate generally good tolerability at doses and exposures in excess of those to be used in humans and provide information regarding signals to be monitored in the clinic. Consistent with the pharmacological activity of idelalisib, lymphoid cell depletion is evident in lymphoid organs of rats and dogs. Bone marrow is a target organ in rats, while liver is a target organ in dogs. idelalisib does not show genotoxicity in a standard battery of nonclinical genotoxicity studies.

Results from an initial Phase 1 study indicated that idelalisib is well tolerated when administered to healthy subjects at doses through 400 mg (the highest dose level tested). This same study also showed that idelalisib is generally well tolerated when administered to healthy subjects at doses through 200 mg twice per day (BID) (the highest dose level tested). When assessed over 7 days in a Phase 1b study in subjects with allergic rhinitis, idelalisib 100 mg BID was also well tolerated; in this study, idelalisib showed clinical and pharmacodynamic activity, attenuating adverse responses to allergenic challenge and decreasing markers of inflammation.

Idelalisib has also been evaluated in a Phase 1 sequential dose-ranging study evaluating once per day (QD) or BID dosing in 191 subjects with lymphoid malignancies including iNHL, mantle cell lymphoma (MCL), and chronic lymphocytic leukemia (CLL). The drug has been symptomatically well tolerated at dose levels through 350 mg BID (the highest dose tested) with several subjects receiving the drug for >2 years. Monitorable, reversible elevations of hepatic transaminases have been observed in some subjects but no maximum tolerated dose (MTD) has been apparent within the tested dose range. Among 34 participating subjects with relapsed or refractory iNHL receiving idelalisib at doses ≥100 mg BID, 20 partial responses have been observed, resulting in a response rate of 59% among subjects with this lymphoma subtype. Substantial activity has also been observed in CLL and MCL. The collective safety, pharmacokinetic, and response data have supported selection of 150 mg BID as an appropriate starting dosing regimen for Phase 2 evaluation. For additional or updated information, please refer to the current version of the Investigator's Brochure.

1.2. Study Design

Idelalisib (Zydelig®) was approved in the United States on July 23, 2014 and in the European Union on September 18, 2014. Refer to local labeling for the approved indication statements.

This protocol describes a Phase 2, open-label, single-arm, 2-stage, efficacy, safety, and pharmacodynamic study of idelalisib in subjects with previously treated iNHL that is refractory both to rituximab and to alkylating-agent-containing chemotherapy.

Eligible subjects will initiate oral therapy with idelalisib at a starting dose of 150 mg BID given continuously. Treatment with idelalisib will continue until tumor progression or unacceptable toxicity. Subjects will be followed in the clinic at 2-week intervals through the first 12 weeks of treatment, at 4-week intervals from 12 to 24 weeks of treatment, at 6-week intervals from 24 to 48 weeks of treatment, and at 12-week intervals thereafter. Tumor response will be evaluated at baseline; at 8, 16, and 24 weeks of therapy; and every 12 weeks thereafter according to standard criteria. The responses will be assessed by both the investigator and an independent review committee (IRC).

The primary objective will be to assess the overall response rate (ORR). Secondary objectives will include determination of duration of response (DOR), lymph node response rate, changes in tumor size, time to response (TTR), progression-free survival (PFS) and overall survival (OS). The findings of the IRC will be considered primary for analyses of ORR, DOR and other tumor control endpoints. Evaluation of health-related quality of life (HRQL) as reported by subjects completing the Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym) and assessment of changes in performance status are also planned. To support the clinical findings, measurement of concentrations of circulating chemokines and cytokines that are reflective of disease activity will be performed. The safety, compliance, and pharmacokinetic profiles of idelalisib will also be assessed.

The study will evaluate the null hypothesis that the IRC-reviewed ORR is ≤20% against the alternative hypothesis that it is ≥39% (ie, ≥~40%). The study will be conducted in 2 stages using Simon's optimal 2-stage design. In Stage 1 of the study, 31 subjects will be enrolled;

if ≥ 9 of these Stage 1 subjects have a tumor response, then the study will continue. In Stage 2, a further 69 subjects will be enrolled. With a total intended sample size of 100 subjects, the study provides a power of >0.90 to achieve a 1-sided significance level of 0.005 and will provide an ample safety database. The final study analysis will be performed when all enrolled subjects have completed efficacy, safety, and other assessments through at least 24 weeks of evaluation.

It is planned that study subjects will be enrolled at investigational sites in North America and Europe. Enrollment is planned to occur over ≤18 months, subject follow-up will continue through ≥6 months, and analysis and reporting will be completed over ~6 months thereafter.

This study is being conducted in support of idelalisib registration. If positive efficacy and safety results are observed, it is intended that the findings would provide the initial basis for regulatory approval of idelalisib as treatment for subjects with iNHL that is refractory to rituximab and to alkylating-agent-containing chemotherapy.

2. INTRODUCTION

2.1. Disease Background – Indolent Non-Hodgkin Lymphoma

NHL comprises a diverse group of malignancies arising in lymphoid tissue. The neoplasms represent a progressive clonal expansion of B cells, T cells, or natural killer cells arising from the accumulation of genetic lesions that affect proto-oncogenes or tumor suppressor genes, resulting in cell immortalization {Friedberg 2008b}. A B-cell origin is documented in 80-85% of cases. Chromosomal translocations that reduce lymphocyte apoptosis are typical. In the United States, NHL is the sixth most common cancer; it is estimated that during the year 2010, ~66,000 new subjects were diagnosed and ~20,000 subjects died of NHL {Jemal 2010}. In Europe, it is anticipated that ~74,000 new cases occured, leading to ~31,000 deaths {Ferlay 2010}. As mortality due to other causes has declined, the incidence of lymphoma has increased; almost exclusively a disease of adulthood, diagnosis most commonly occurs during in subjects between 50 and 70 years of age {Friedberg 2008b}.

Of the B-cell NHLs, 4 subtypes (follicular lymphoma [FL], small lymphocytic lymphoma [SLL], lymphoplasmacytoid lymphoma [LPL] - with or without Waldenström macroglobulinemia [WM], and marginal zone lymphoma [MZL]) have differing pathological features {Campo 2011}, but are generally included among those characterized as indolent in nature because they have common clinical presentations, show a slowly progressive natural history, and generally require similar treatments {Pileri 2004}. Subjects with iNHL typical present with painless and gradually progressive peripheral adenopathy {Friedberg 2008b, Salles 2007}. Some subjects may experience primary extra-nodal involvement or B symptoms (ie, temperature > 38°C, night sweats, or weight loss > 10% from baseline within 6 months). As the disease advances, fatigue is often noted. Bone marrow involvement is common and may result in cytopenias. Subjects with iNHL commonly have splenomegaly and hepatomegaly. Elevated serum levels of lactate dehydrogenase (LDH) reflect general tumor burden. Abnormal transaminase values may indicate hepatic involvement or chronic lymphoma-related inflammation.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the neck, chest, abdomen, and pelvis, as well as bone marrow aspirate and biopsy, are employed to stage iNHL {Zelenetz 2010}. Positron-emission tomography (PET) is sometimes used to identify occult sites of disease in subjects who appear to have localized iNHL based on CT and bone marrow biopsy {Seam 2007}. The Ann Arbor staging system categorizes subjects by whether they have single sites of involvement (Stage 1), ≥2 sites of disease on the same side of the diaphragm (Stage 2), sites of disease on both side of the diaphragm (Stage 3), or disseminated disease (Stage 4) {Lister 1989} (Appendix A). For follicular iNHL, the Follicular Lymphoma International Prognostic Index (FLIPI) has been developed to define outcomes {Solal-Celigny 2004} (Appendix B). The FLIPI characterizes subjects in terms of 5 adverse prognostic factors; age >60 years, Ann Arbor stage III-IV, hemoglobin<12 g/dL, number of nodal areas >4, and serum LDH above normal. Subjects are scored as low risk (≤1 factor), intermediate risk (2 factors), or high risk (≥3 factors). While a protracted course is common in iNHL, life expectancy varies by the types of factors represented in the FLIPI score; median survival is ~4 to >10 years from diagnosis depending upon such prognostic characteristics {Solal-Celigny 2004}. Subjects are at risk of transformation

of iNHL to aggressive, diffuse, large B-cell lymphoma (DLBCL) at a rate of 2 to 3% per year {Bastion 1997, Montoto 2007}; such transformation is usually associated with a poor clinical outcome.

Radiation therapy to involved sites is the most common treatment for the infrequent subjects with localized iNHL (Stage 1 or non-bulky Stage 2 disease) {Wilder 2001}, {Tsang 2005}. Systemic therapy is considered for the majority of subjects with iNHL, in whom extensive lymphoma (Stage 2 bulky, Stage 3, or Stage 4 disease) is present {Zelenetz 2010}. Watchful waiting is possible but subjects are generally treated if they have lymphoma-related symptoms or end-organ dysfunction, bulky disease, cytopenias, persistent disease progression, or a strong preference for immediate therapy. Because iNHL requiring systemic therapy is essentially incurable and subjects may be older and have comorbidities, the goal of therapy is primarily to alleviate lymphoma-related symptoms and prolong progression-free interval.

For older or infirm subjects, single-agent rituximab (Rituxan®) or alkylating agents such as cyclophosphamide or chlorambucil may be administered {Zelenetz 2010}. Most subjects receive chemoimmunotherapy in which rituximab is given together with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) {Buske 2009, Hiddemann 2005} or cyclophosphamide, vincristine, prednisone (R-CVP) {Marcus 2005, Marcus 2008}. Alternative regimens includes rituximab with the alkylating agent, bendamustine, or fludarabine- or mitoxantrone-based therapy that may include an alkylating agent {Herold 2007, Zinzani 2004}. Meta-analysis data from randomized trials indicate that the addition of rituximab to chemotherapy not only improves tumor control but also extends overall survival (OS) in previously untreated subjects {Schulz 2007}. Based on controlled trials, rituximab has formal regulatory approval for use as a component of front-line chemoimmunotherapy of iNHL. In addition, maintenance or consolidation therapy with rituximab or yttrium^{90}-ibritumomab tiuxetan (Zevalin®) has been shown to prolong PFS {Morschhauser 2008, van Oers 2007, Vidal 2009}.

Despite the chemosensitivity of iNHL to front-line therapy, existing systemic therapies for iNHL are not curative. Some subjects will be refractory to initial therapy and most subjects will ultimately relapse. Several treatments have received regulatory approval in the United States and/or Europe for treatment of refractory or relapsed disease, including rituximab, yttrium^{90}-ibritumomab tiuxetan, iodine^{131}-tositumomab (Bexxar®), and bendamustine (Treanda®). The principal support for use in these settings has comprised non-randomized single-arm trials that have focused on documenting treatment-related tumor responses in populations of subjects with disease that has become resistant to either alkylating agents or rituximab immunotherapy {Cheung 2009, Ferrucci 2010, Fisher 2005, Friedberg 2008a, Horning 2005, Johnston 2010, Kahl 2010, Kaminski 2000, Kaminski 2005, Kaminski 2001, Maloney 1997, McLaughlin 1998, Piro 1999, Schilder 2004, Vose 2000, Witzig 2002}. Yttrium^{90}-ibritumomab tiuxetan and iodine^{131}-tositumomab use has been limited because of medical and practical restrictions on the use of these agents; these drugs are contraindicated in subjects with substantial pre-existing myelotoxicity or bone marrow lymphoma involvement and their use is constrained by the complexity of dosimetry calculations and drug preparation, the need for administration by specifically trained clinicians at specially equipped sites, protracted Grade 3-4 hematological toxicity that commonly results in infectious complications and impedes subsequent therapy, and long-term risks of hypothyroidism.

Other approaches that may be attempted off-label include alkylating agent monotherapy, alkylating-agent-based combination therapy (CVP, CHOP), or administration of purine analogues (fludarabine, cladribine) {Zelenetz 2010}. Similarly, subjects may be treated off-label with bortezomib (Velcade®) or lenalidomide (Revlimid®) {Di Bella 2010, Goy 2005, Witzig 2009}.

Due to the acquisition of drug resistance, progressively less activity is observed, particularly when administering previously used therapies; the disease course is characterized by a continuous decrease in the quality and the duration of tumor response with each subsequent treatment {Salles 2007}. Subjects face the burden of cumulative myelosuppressive toxicity, a problem that has been documented with fludarabine {Janikova 2009} and commonly limits continued therapy with cytotoxic agents such as bendamustine {Friedberg 2008a, Kahl 2010}. In addition, there is a well-document risk of myelodysplasia and/or acute myelogenous leukemia associated with use of alkylating agents, doxorubicin, fludarabine, iodine^{131}-tositumomab, and Y^{90}-ibritumomab tiuxetan {Friedberg 2006}. Consequently, new therapies with novel mechanisms of action are needed to offer additional treatment options for subjects with iNHL. The need is especially acute in those subjects whose disease has become refractory to existing chemoimmunotherapeutic approaches, particularly in those with lymphoma that is refractory to both rituximab and alkylating agents.

2.2. Role of Phosphatidylinositol 3-Kinases in Tumor Pathogenesis

Class I PI3Ks are a family of intracellular signaling proteins that are essential components of migratory, proliferative, survival, and differentiation pathways in many cell types, including those of hematopoietic origin [reviewed in {Okkenhaug 2003b}]. These enzymes consist of a regulatory subunit (designated p50, p55, p85, or p101) and a catalytic subunit (designated p110α, p110β, p110δ, or p110γ). Upon PI3K activation, p110 generates the key lipid second messenger phosphatidylinositiol (3,4,5)-trisphosphate (PIP3) through phosphorylation of the 3 position of the inositol head group of phospholipids present in the cell membrane. PIP3 acts as a binding site for recruitment and activation of numerous intracellular signaling enzymes. The most important of these is the serine/threonine kinase, AKT, which mediates a positive pleotropic effect on cell survival, proliferation, growth, and metabolism {Engelman 2006}. Also important in B lymphocytes is the Bruton tyrosine kinase (BTK), that plays an essential role in antigen receptor signaling. The activity of PI3K is opposed by lipid phosphatases that include phosphatase and tensin homolog (PTEN), a known tumor suppressor that is expressed in all cells and inositol polyphosphate 5-phosphatase (SHIP), an enzyme that is expressed in hematopoietic cells.

PI3Kδ shows an expression pattern that is largely restricted to cells of hematopoietic origin {Vanhaesebroeck 2005}. Mice deficient in PI3Kδ have no gross abnormalities, are fertile, fecund, and live a normal life span without an increased susceptibility to infections {Okkenhaug 2003a}. However, effects on intracellular signaling, proliferation, migration, and differentiation have been observed in cells of myeloid and lymphoid lineages {Sujobert 2005}. In particular, the B-lymphocyte population in these animals shows a decrease in maturation, diminished receptor-induced proliferation, and increased susceptibility to apoptotic cell death.

The converse situation exists in B-cell malignancies. In this circumstance, B-cell receptor activation and/or stimulation by proliferation and survival factors present in lymph node and bone marrow microenvironments aberrantly elevate PI3K signaling {Bernal 2001, Munk Pedersen 2004, Petlickovski 2005}. Genetic and pharmacological interventions have shown that factors such as antigen, CD40 ligand, BAFF, CXCL12, and CXCL13 all stimulate B-cell proliferation and survival via a PI3K-dependent pathway {Durand 2009, Lannutti 2011, Okkenhaug 2002}. A survey of multiple lymphoma cell lines showed uniform expression of PI3Kδ and in many cases constitutive activation of the PI3K pathway as indicated by expression of phosphorylated AKT {Lannutti 2011}. Collectively, these data have supported targeting PI3Kδ in subjects with B-cell malignancies to decrease aberrant lymphocyte activation and function, reduce excessive lymphocyte proliferation, and enhance apoptosis of transformed B cells.

2.3. Development of Idelalisib

Knowledge of the critical importance of PI3Kδ in B-cell biology and neoplasia has encouraged the development of drugs to inhibit this enzyme as a therapy for lymphoid malignancy. Gilead Sciences, a pharmaceutical company located in Seattle, WA, USA, has used high-throughput screening to identify novel agents that selectively inhibit PI3Kδ function. Chemical optimization, pharmacological characterization, and toxicological evaluation have led to identification of idelalisib, an orally bioavailable, new chemical entity that potently blocks PI3Kδ activity and diminishes lymphoma growth and survival.

2.4. Nonclinical Characterization of Idelalisib

2.4.1. Drug Substance and Formulation

Idelalisib is a fluorinated quinazolinone with 1 stereogenic center. Idelalisib is the *S* enantiomer. The compound has no known structural similarity to existing drugs. The drug substance is a white to off-white, crystalline powder with a chemical formula of $C_{22}H_{18}FN_7O$, a molecular weight of ~415 Daltons, and low aqueous solubility. Idelalisib is orally bioavailable. For toxicological and clinical testing, Idelalisib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

2.4.2. Efficacy Pharmacology

Nonclinical efficacy pharmacology data in enzyme-based and cell-based systems indicate that idelalisib is a potent inhibitor of PI3Kδ but that its selectivity spares other PI3K isoforms and other kinases. Testing in nonclinical models of lymphoid neoplasia confirm the importance of the PI3Kδ pathway in these tumor types, and document idelalisib activity in suppressing in the growth and survival of these malignancies.

2.4.2.1. Potency and Selectivity

In in vitro assays evaluating PI3K enzymatic activity, idelalisib potently inhibited PI3Kδ, with an IC_{50} value of 2.5 nM. By contrast, IC_{50} values for the effects of idelalisib on PI3Kα, PI3Kβ, and PI3Kγ were 820, 565, and 89 nM respectively, indicating a selectivity of idelalisib for PI3Kδ

that is 40- to 300-fold greater than for other PI3K Class I family members. When assessing IC_{50} values relative to Class II, III, and IV PI3K enzymes, idelalisib showed 400- to 4000-fold greater activity for Class I PI3Kδ inhibition. In vitro selectivity was further demonstrated by evaluation of activity against the comprehensive panel of 402 kinases in the Ambit KinomeScan; idelalisib at 10 μM (0.42 μg/mL) inhibited PI3K enzymes but showed no activity against other enzymes.

Potency and selectivity have been confirmed in cell-based in vitro assays. In human whole blood, idelalisib potently inhibited basophil activation via a PI3Kδ-dependent pathway, with an EC_{50} of 62 nM; by contrast, inhibition of basophil activation via a PI3Kγ-dependent pathway showed an EC_{50} of 4,456 nM. idelalisib also showed potent *in vitro* inhibition of PI3Kδ-mediated processes in other cell types; activation of human B-cell proliferation via the B-cell receptor, neutrophil degranulation in response to bacterial peptide, and stimulation of human T-cell proliferation via the T-cell receptor were inhibited with respective EC_{50} values of 8 nM, 119 nM, and 932 nM. By contrast, when examining PI3Kα- or PI3Kβ-mediated phosphorylation of AKT in primary mouse fibroblasts, idelalisib showed EC_{50} values of > 20 μM and 1900 nM, thus substantiating the lack of idelalisib effect on signaling via these PI3K isoforms.

2.4.2.2. Activity in Models of Lymphoid Malignancy

Evaluation of the PI3K expression pattern in lymphoid malignancies has supported use of idelalisib to target PI3Kδ as therapeutic approach to these cancers {Lannutti 2011}. In fresh isolates from human subjects, primary B-cell acute lymphocytic leukemia (ALL) cells and CLL cells showed high levels of PI3Kδ and PI3Kγ relative to those seen in normal peripheral blood mononuclear cells (PBMCs). By contrast, PI3Kα and PI3Kβ were only variably expressed. Similarly, a panel of cell lines representing a variety of B-cell malignancies, including B-cell ALL, FL, MCL, and DLBCL, showed consistent high-level expression of PI3Kδ. There appeared to be functional consequences of this over-expression; in primary B-cell ALL, CLL, and MCL tumor cells and in leukemia and lymphoma cell lines, phosphorylated AKT was constitutively present when assessed by flow cytometry or Western blot analysis. These data demonstrate that PI3Kδ is highly expressed in B-cell malignancies and that constitutive PI3K pathway activation is a common event in B-cell tumors.

Primary CLL and MCL subject samples and B-cell ALL, FL, and DLBCL cell lines that were positive for phosphorylated AKT expression have been used to evaluate the effect of PI3Kδ inhibition by idelalisib {Herman 2010, Lannutti 2011}. In primary cells, idelalisib treatment induced a dose-dependent reduction in phosphorylated AKT with EC_{50} values of <100 nM in all samples evaluated. In cell lines, EC_{50} values of 0.1 to 1.0 μM were observed, confirming a central role for PI3Kδ in constitutive PI3K signaling in malignant B cells, and the activity of idelalisib in suppressing this pathway.

To evaluate the role of PI3Kδ in mediating signals from the tumor microenvironment, primary tumor cells and cell lines were pretreated with increasing concentrations of idelalisib or vehicle and then stimulated with CXCL13 (CXCR5 activation), CXCL12 (CXCR4 activation), anti-IgM (B-cell receptor [BCR] activation), BAFF (BAFFR activation) or soluble CD40 ligand

(CD40 activation) {Lannutti 2011}. Activation via any of these pathways could be inhibited by idelalisib at EC_{50} values of <100 nM, suggesting that idelalisib can interrupt signals from the tumor microenvironment that are essential for the expansion, homing, and survival of malignant B cells and that promote resistance to conventional drug therapy.

The tumoricidal activity of idelalisib has also been documented in preclinical models of lymphoid malignancy. When primary CLL cells were incubated with idelalisib at a concentration of 10 μM for 96 hours, median [range] cell survival was 36% [26-78%] relative to vehicle-treated cells. In B-cell ALL, FL, DLBCL, and MCL cell lines, concentration-dependent cell killing was uniformly observed during 72-hour incubations with idelalisib at concentrations of 0.1 to 5 μM. Tumor cell killing by idelalisib were associated with 3- to 5-fold increases in Annexin-V staining, and 2- to 8-fold increases in cleaved caspase 3 and cleaved Poly (ADP-ribose) polymerase (PARP) expression, providing documentation of drug-induced apoptosis {Lannutti 2011, May 2008}.

2.4.3. Safety Pharmacology

In vitro and in vivo safety pharmacology studies with idelalisib demonstrate a generally favorable non-clinical safety profile. These studies indicate that the drug may slow bone marrow progenitor proliferation and differentiation and that it has expected effects on B-cell response to antigen challenge. However, the data indicated that idelalisib is unlikely to cause serious off-target effects or adverse effects on critical organ systems. Idelalisib has no meaningful effect on the human ether-à-go-go-related gene (hERG) channel, indicating that idelalisib would not be expected to induce clinical QT prolongation.

The drug has also proved well tolerated in standard in vivo Good Laboratory Practice (GLP) studies of pharmacological safety. A functional observation battery in rats revealed no adverse effects on behavior or on autonomic, neuromuscular, or sensorimotor function. In a cardiopulmonary function study in awake, telemeterized male beagle dogs, single doses of idelalisib induced no meaningful abnormalities in pulmonary, cardiovascular, arterial blood gas, or electrocardiographic (ECG) (including QT interval) parameters. In an assessment of bacterial challenge in rats, idelalisib enhanced, rather than impaired, the phagocytic host clearance of staphylococcal bacteria.

2.4.3.1. In Vitro Evaluation of Off-Target Effects

To assess the potential for adverse off-target effects, idelalisib was evaluated against primary molecular targets in radioligand displacement assays. These assays measure functional binding interactions for 68 cell proteins that include G-protein-coupled receptors, ion channels, receptor tyrosine kinases, steroid receptors, and transporters. Idelalisib at concentration of 10 μM (4.2 μg/mL) did not significantly inhibit binding of any of the radioligands tested. When taken together with the efficacy pharmacology data, these results support the selectivity of idelalisib.

The effect of idelalisib on human ether-à-go-go-related gene (hERG) channel activity was investigated. Testing was performed using a rubidium flux-based method in HEK293 cells stably transfected with hERG. No significant hERG inhibition was observed at idelalisib concentrations through 50 μM (21 μg/mL) (the highest concentration tested), indicating that idelalisib would not be expected to induce clinical QT prolongation.

Potential inhibitory effects of idelalisib on bone marrow function were assessed. Rat-derived bone marrow cultures were evaluated for erythroid precursors by flow cytometry and quantification of erythroid blast-forming units (BFU-e). Idelalisib did not significantly inhibit erythroid differentiation at 0.1 or 1 μM (0.04 or 0.42 μg/mL), either in the presence or absence of erythropoietin. At a concentration of 10 μM (4.2 μg/mL), idelalisib decreased progression of erythroid differentiation, and at concentrations of 10 and 100 μM (4.2 and 42 μg/mL), idelalisib decreased BFU-e values, both in the presence or absence of erythropoietin. Potential idelalisib effects on human bone marrow were assessed in bone marrow cultures derived from healthy volunteers. When evaluated by flow cytometry and colony-forming assays, idelalisib across a range of concentrations from 0.1 to 50 μM (0.04 to 21 μg/mL) showed concentration-dependent effects on erythroid, myeloid, and megakaryocytic differentiation in the presence or absence of erythropoietin. While idelalisib is not cytotoxic to bone marrow, these data suggest that idelalisib may suppress generation of red cells, neutrophils, and platelets when administered at supratherapeutic doses.

2.4.3.2. In Vivo Evaluation for Immune, Neurologic, and Cardiopulmonary Effects

To evaluate effects on T-cell-independent, B-cell immunization, rats were inoculated with sheep red blood cells at 4 hours after beginning a 10-day course of idelalisib at doses of 1, 3, 10, 30, and 150 mg/kg BID. When assessed at 7 and 10 days after antigen challenge, idelalisib at lower doses of 1 or 3 mg/kg BID did not impede IgM or IgG antibody response. However, rats receiving higher idelalisib doses of 10, 30, and 150 mg/kg BID showed no IgM or IgG antibody responses at these same timepoints. In an alternative assessment of its effects on primary antibody response, idelalisib at a dose of 60 mg/kg BID was administered to rats for 3 days before and for 14 days after antigen challenge with dinitrophenol-keyhole limpet hemocyanin (DNP-KLH). When assessed at 7, 10, and 14 days after antigen challenge, idelalisib administration dampened IgM and IgG antibody responses. In a similar assessment of secondary antibody response, rats who had shown a primary antibody response to DNP-KLH challenge 18 weeks previously underwent a DNP-KLH rechallenge at 4 hours after beginning a 7-day course of idelalisib at a dose of 60 mg/kg BID. When assessed 8 days after rechallenge, idelalisib was associated with nearly complete suppression of secondary IgM and IgG antibody responses to DNP-KLH. Collectively, these data suggest that high doses of idelalisib may be associated with blunting of primary and secondary B-cell-mediated antibody responses to immunization.

In an assessment of host response to bacterial challenge, idelalisib at doses of 30, 60, and 120 mg/kg was administered 1 hour before and 12, 24, and 36 hours after inoculation of Staphylococcus aureus into the inguinal region of male rats. At 48 hours post-infection, colony counts from groin abscesses showed dose-dependent inhibition of staphylococcal colonies by 65 to 85% among idelalisib-treated animals relative to control animals. By contrast, the positive control – dexamethasone at 2 mg/kg – increased bacterial colony counts by 351% relative to the vehicle control. Thus, idelalisib appeared to enhance, rather than impair, the phagocytic host clearance of bacteria in this model.

Idelalisib has also proved well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacological safety. A functional observation battery in Sprague-Dawley rats dosed with a single oral dose at idelalisib dose levels of 50, 100, or 150 mg/kg revealed no adverse effects on behavior or on autonomic, neuromuscular, or sensorimotor function at any dose level. In a cardiopulmonary function study in awake telemeterized male beagle dogs, single

doses of idelalisib by oral gavage at dose levels of 1, 5, and 20 mg/kg induced no meaningful changes in pulmonary, cardiovascular, arterial blood gas, or electrocardiographic (ECG) (including QT interval) parameters.

2.4.4. Pharmacokinetics and Drug Metabolism

Consistent with the moderate to high bioavailability seen in nonclinical species, idelalisib shows high permeability across human Caco-2 cell monolayers. At lower concentrations, the reverse permeability at low concentration exceeds forward permeability, indicating efflux driven by transporters (eg., human P-glycoprotein [MDR1] and breast cancer resistance protein [BCRP]); idelalisib is a substrate for the efflux transporters MDR1 and BCRP; however, the permeability increases in a concentration-dependent manner, resulting in a lower efflux ratio at higher, clinically relevant concentrations of idelalisib.

Idelalisib exhibits moderately high plasma protein binding in mouse, rat, dog, and human. In dog and human plasma, the protein binding is concentration-independent between 1 and 20 μM. Protein binding in human plasma is slightly higher than in mouse, rat, and dog plasma, which have comparable free fractions. In human plasma, idelalisib and GS-563117 (a metabolite of idelalisib) have an average free fraction of ~16% and ~12%, respectively.

After oral administration of [^{14}C]idelalisib to rats and dogs, radioactivity is widely distributed, but relatively excluded from bone, brain, spinal cord, and eye lens in rats and from brain and eyes in dogs. In rats, the radioactivity declines steadily and most tissues have undetectable levels by 72 hours post dose. In bile duct-cannulated rats and dogs, ≥ 69% of radioactivity is recovered in bile and urine, indicating high absorption of idelalisib in vivo.

In hepatic tissues from nonclinical species, idelalisib is primarily metabolized by aldehyde oxidase, with some involvement of CYP3A and UGT1A4. In vitro metabolism in dog and human yields 3 primary oxidative metabolites and 5 primary glucuronides. Of these, the oxidative product GS-563117 is the predominant metabolite in vitro and in vivo. In preclinical species, plasma levels of GS-563117 are below those of idelalisib. In humans, GS-563117 (only circulating metabolite) plasma levels exceed those of idelalisib. After oral administration of [^{14}C]idelalisib to rats and dogs, biliary excretion appears to be the major route of elimination of idelalisib and its metabolites as the majority of radioactivity is found in feces or bile and little in urine.

Idelalisib is substrate for the efflux transporters MDR1 and BCRP, but not a substrate for the renal transporters OCT2, OAT1, and OAT3 or the hepatic uptake transporters OATP1B1 and OATP1B3. GS-563117 is a substrate for MDR1 and BCRP, but not a substrate for OATP1B1 and OATP1B3.

Idelalisib is not an inhibitor of CYP1A, CYP2B6, CYP2C9, and CYP2D6, and at concentrations above those observed clinically, is an inhibitor of CYP2C8 (IC_{50} = 13 μM), CYP2C19 (IC_{50} = 76 μM), and CYP3A (IC_{50} = 44 μM). GS-563117 is not an inhibitor of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and a reversible and time dependent inhibitor of CYP3A (IC_{50} = 3.1 μM), (K_I = 0.18 μM, k_{inact} = 0.033 min^{-1} with midazolam as the probe substrate).

In vitro, idelalisib is not an inhibitor of the transporters BCRP, OCT2, OAT1, and OAT3, and is an inhibitor of MDR1 (IC_{50} = 7.7 μM), OATP1B1 (IC_{50} = 10.1 μM), OATP1B3 (IC_{50} = 7.0 μM), and, at concentrations above those observed clinically, of glucuronosyltransferase UGT1A1 (IC_{50} = 42.0 μM). GS-563117 is not an inhibitor of MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, and at concentrations above those observed clinically, an inhibitor of UGT1A1 (IC_{50} = 16.8 μM).

Idelalisib does not activate human AhR or induce CYP1A2 (mRNA or activity) at clinically relevant concentrations. Idelalisib is a weak activator of human PXR (EC_{50} = 18 μM) and shows similarly weak potency as an inducer of CYP3A4, CYP2C8, CYP2C9, UGT1A1, and MDR1 (by mRNA). Approximately 2-fold weaker induction of CYP2B6 activity and mRNA suggests weak activation of CAR. GS-563117 shows no induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A, UGT1A1, UGT1A4, MDR1, and aldehyde oxidase at clinically relevant concentrations.

Any potential clinical implications of these metabolism studies are being evaluated in a formal drug-drug interaction study (GS-US-313-0130) which is evaluating the effect of idelalisib on cytochrome P450 3A and the drug transporters P-gp, OATP1B1, and OATP1B3.
Study GS-US-313-0130 will also evaluate the impact of an inducer of metabolizing enzymes and transporters (rifampin) on the PK of idelalisib in healthy human subjects. Preliminary findings from this study are presented in Section 2.5.3.

2.4.5. Toxicology

A comprehensive package of nonclinical studies has been conducted and provides a toxicological profile of idelalisib in support of the treatment of adults with advanced cancer. The following toxicology studies have been conducted to assess the safety of idelalisib: single-dose (in rats and dogs) and repeat-dose oral toxicity studies (up to 26 weeks in rats and up to 39 weeks in dogs), in vitro and in vivo genotoxicity studies, and developmental and reproductive toxicity studies (fertility and embryo-fetal development in rats).

Once daily administration of idelalisib was associated with B-cell depletion in numerous lymphoid organs in rats and dogs, consistent with the known pharmacology of PI3Kδ inhibition {So 2012}. All changes were partially or completely reversible following a 4-week recovery period. Serum transaminase elevations were noted in the dog in both the 28-day and 13-week studies at doses ≥ 7.5 mg/kg/day. Peak elevations occurred approximately 4 weeks following initiation of dosing and resolved completely with continued dosing. No evidence of chronic hepatic injury was noted in either the 13- or 39-week studies at dose levels up to 7.5 mg/kg/day (Day 272 AUC_{0-t} 17.1 μg·hr/mL). In an investigative pharmacology study, a further characterization of the pattern of serum transaminase changes associated with administration of 15 mg/kg/day of idelalisib to dogs confirmed hepatic adaptation to the effect. In this study, mean serum ALT/AST values peaked at approximately Day 24 to Day 27 and resolved spontaneously as the dogs continued on idelalisib through the end of the study on Day 44.

Decreased testes weights were observed in GLP repeat dose studies in rats and dogs. Decreased testicular weights were noted in all studies. A male fertility in rats study indicated that there was no impact on fertiliy or reproductive potential following daily dosing for 10-weeks prior to

100 mg/kg/day. Spermatogenic assessment of idelalisib treated animals was similar to controls. Changes in testicular weight in repeat dose studies are suspected to be associated with fluid production and/or tubular contraction and not a degenerative effect.

Pregnant female rats were administered idelalisib in a standard embryo-fetal development toxicity study at oral doses up to 150 mg/kg/day. Idelalisib was shown to be embryo lethal and teratogenic in rats at ≥ 75 mg/kg/day (Gestation Day 17 AUC_{0-t} 251 µg hr/mL). Dose-dependent developmental findings included decreased fetal viability, increased early and late resorptions, and decreased mean fetal body weights. Dose-dependent external malformations included short tails and complete tail loss. Additional external malformations were single instances of hydrocephaly and microphthalmia, occurring in separate fetuses from different litters.

Idelalisib was negative for mutagenic potential in a bacterial reverse-mutation test and negative for inducing chromosomal aberrations in cultured human peripheral blood lymphocytes. Idelalisib has shown some evidence of inducing micronuclei in this in vivo test system when tested at high dose levels, up to the standard limit of 2000 mg/kg. However, based on the mechanism of action of PI3Ks and their role as intracellular signaling proteins essential to migratory, proliferative, survival, and differentiation pathways, idelalisib may cause a small increase in micronucleated erythrocytes by mechanisms unrelated to the inherent genotoxicity of the compound {Tweats 2007}. These data suggest that idelalisib is not genotoxic.

Coadministration of cyclophosphamide with idelalisib did not appear to exacerbate the myelosuppressive effects of cyclophosphamide. Idelalisib did not impair bacterial clearance in a rat *S. aureus* abscess model.

A phototoxicity study yielded inconclusive results for the assessment of idelalisib due to cytotoxicity observed in the assay. However, the predominant oxidative metabolite, GS-563117, was determined to be toxic only in the presence of ultraviolet A (UVA) light.

2.5. Clinical Experience with Idelalisib

Idelalisib has undergone extensive early clinical evaluation in a series of Phase 1 studies in healthy volunteers and subjects. Studies in healthy subjects have provided information on drug safety; pharmacokinetics; food effects; the potential for drug interactions with CYP3A inhibitors; and idelalisib absorption, metabolism and excretion {Webb 2010}. A Phase 1 study in subjects with allergic rhinitis has offered additional safety information and confirmed the expected immunomodulatory pharmacological effects of the drug. A Phase 1 study in subjects with lymphoid malignancies has extended safety and pharmacokinetic observations; documented the clinical and pharmacodynamic activity of idelalisib in subjects with iNHL, MCL, and CLL; and provided dosing information in support of further development {Furman 2010, Kahl 2010}.

Reference the Investigator Brochure for updated information regarding clinical experience with idelalisib.

2.5.1. Phase 1 Single- and Multiple-Dose Study in Healthy Volunteers (Study 101-01)

This first-in-human study was performed to evaluate the safety, pharmacokinetics, and pharmacodynamics of idelalisib. Five cohorts of healthy male subjects were enrolled to receive sequentially higher single doses of idelalisib at dose levels of 17, 50, 125, 250, or 400 mg. Subsequently, 3 cohorts of healthy male subjects were enrolled to receive sequentially higher multiple doses of idelalisib given over 7 days at 50 mg BID, 100 mg BID, or 200 mg BID. Within each cohort, 2 subjects were randomized to placebo and 6 subjects to idelalisib.

A total of 8 cohorts or 64 subjects were enrolled to the trial, as planned. Idelalisib treatment was well tolerated. There were no serious or severe adverse events. A maculopapular skin rash affecting the trunk and extremities was observed in 3/6 subjects who received idelalisib at 200 mg BID for 7 days. The rash resolved spontaneously 5 to 11 days later. Drug rechallenge in 2 of these subjects resulted in recurrence in 1 subject who received 200 mg BID for 5 days and in no recurrence in 1 subject dosed at 100 mg BID for 7 days. The rechallenge rash was also maculopapular in nature and resolved over 10 days during treatment with topical corticosteroids. Skin biopsies showed spongeotic dermatitis with perivascular infiltrates containing lymphohistiocytes and eosinophils. The data suggested that the rash represented a delayed-type hypersensitivity reaction. There were no other adverse events that were suggestive of a causal relationship with idelalisib treatment. No clinically significant abnormal findings were observed in vital signs, ECGs, or clinical laboratory tests.

Pharmacokinetic results indicated that idelalisib appeared rapidly in plasma with a median T_{max} of 1 to 1.5 hours. C_{max} and AUC increased in a less-than-dose-proportional manner and mean $t_{1/2}$ values were across the dose range were 6.5 to 9.8 hours.

An ex-vivo pharmacodynamic evaluation was performed on whole blood in subjects receiving 200 mg BID. Anti-FCεR1 was used to activate basophils via the PI3Kδ pathway. Idelalisib administration was associated with inhibition of basophil activation as measured by CD63 surface expression.

2.5.2. Phase 1 Safety and Pharmacodynamic Study in Subjects with Allergic Rhinitis (Study 101-04)

This randomized, double-blind, placebo-controlled, 2-period crossover study was designed to evaluate the safety, clinical, and pharmacodynamic effects of idelalisib in male subjects with allergic rhinitis. Subjects with documented allergy to grass pollen upon screening allergen exposure were randomized to placebo or idelalisib at a dose of 100 mg BID for 7 days. On the last day of dosing, subjects were exposed to allergen in an environmental chamber for 4 hours. During the allergen challenge, symptoms, nasal airflow, and nasal secretions were measured. Following a 2-week washout period, subjects received the alternative treatment for 7 days and again underwent allergen challenge and evaluation.

Altogether, 41 male subjects were enrolled and 39 subjects completed the study. One subject withdrew for personal reasons and 1 subject receiving placebo was withdrawn after having elevations in muscle-derived enzymes following strenuous exercise. Idelalisib was well tolerated. Two subjects reported mild adverse events that were not considered to be related to study drug. No rash was observed. There were no clinically significant laboratory abnormalities.

Idelalisib treatment led to statistically significant reductions in the primary efficacy endpoint of total nasal symptom score. Significant reductions were also achieved in total symptom score, nasal airflow, and nasal secretion weight. An ex-vivo pharmacodynamic evaluation was performed on whole blood collected on Day 1. In response to grass antigen, basophil activation was assessed by measurement of % CD63+/CCR3+ cells using flow cytometry. Idelalisib administration induced significant inhibition of basophil activation with mean post-dose decreases of 76% at 1.5 hours and 66% at 3 hours. By contrast, placebo had no effect.

2.5.3. Phase 1 Study Evaluating Food-Effect, Drug-Drug Interactions, and Metabolism in Healthy Volunteers (Study 101-05)

This 3-period crossover study was designed to evaluate food effects on idelalisib pharmacokinetics, assess the effect of ketoconazole (a potent CYP3A inhibitor) on idelalisib pharmacokinetics, and to evaluate idelalisib absorption, metabolism and excretion after a single oral or intravenous microdose of [^{14}C]idelalisib. In the first period, subjects received a single 400-mg idelalisib dose in either fasting or fed states; subjects dosed in the fasting state also received an oral microdose of [^{14}C]idelalisib. In the second period, subjects received a single 400 mg idelalisib dose in either fasting or fed states, alternate to the condition during the first period; subjects dosed in the fasting state also received an intravenous microdose of [^{14}C]idelalisib. In the third period, all subjects received ketoconazole 400 mg QD for 4 days and on the fourth day also received a single 400-mg idelalisib dose in the fasting state.

Twelve subjects were enrolled and 11 subjects completed the study. One subject had musculoskeletal pain and muscle-related increases in serum creatine kinase (CK), ALT, and AST and was discontinued prior to the third study period. Idelalisib treatment was well tolerated throughout the study and no idelalisib-related adverse events or laboratory abnormalities were noted.

Compared to fasted dosing, ingestion of a high-fat, high-calorie meal just prior to administration of idelalisib increased the median T_{max} from 0.75 hours to 3 hours without altering mean C_{max}. The aggregate effect was a modest increase of 1.4-fold in mean AUC, which is not considered to be clinically relevant; thus, idelalisib may be given with or without food.

Idelalisib is metabolized in humans primarily by aldehyde oxidase, with some involvement of CYP3A4 and UGT1A4. Accordingly, when idelalisib was administered following 4 days of ketoconazole dosing, moderate increases in mean idelalisib C_{max} and AUC values of 30% and 80%, respectively, which is not considered to be clinically relevant and suggesting that idelalisib is a weak CYP3A substrate. GS-563117 is formed from idelalisib primarily via aldehyde oxidase.

The ^{14}C-labeled idelalisib human mass balance results showed that the drug has a moderate to high oral bioavailability. Idelalisib is eliminated mainly via hepatic metabolism and biliary excretion in the feces (~78% of dose); recovery in urine was < 15%. GS-563117 was the only circulating metabolite observed in human plasma and was also observed in urine and feces.

Preliminary results from the drug interaction/probe Study GS-US-313-0130 indicate that idelalisib does not affect the pharmacokinetics of substrates of Pgp, BCRP, OATP1B1 or OATP1B3 transporters. Idelalisib is not expected to affect the exposures of coadministered agents via transporter mediated interactions.

The exposures (AUC) of probe CYP3A substrate, midazolam, increased ~5-fold upon coadministration with idelalisib, driven by reversible and time-dependent CYP3A inhibition by GS-563117, the only circulating metabolite of idelalisib. Coadministration of the highly potent CYP3A inducer rifampin resulted in a ~75% reduction in idelalisib systemic exposures, likely driven by a higher relative contribution to CYP3A to overall idelalisib clearance under the induced state.

2.5.4. Phase 1 Study in Subjects with Relapsed or Refractory Hematologic Malignancies (Study 101-02)

This Phase 1 dose-ranging study was designed to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of idelalisib in subjects with relapsed or refractory hematologic malignancies {Furman 2010, Kahl 2010}. Dose-ranging has been performed across progressively higher dose levels in sequential cohorts of 3 to 6 subjects with B-cell NHL or CLL. During the study, expansion of cohorts has also permitted evaluation in subjects with AML and multiple myeloma (MM). Single-agent idelalisib has been administered at starting dose levels of 50 mg BID, 100 mg BID, 150 mg BID, 200 mg BID, 350 mg BID and 300 mg QD. Patients have received idelalisib continuously and have been evaluated in cycles of 28 days. Idelalisib administration has been continued until the earliest of disease progression, intolerable toxicity, or completion of 12 cycles of therapy (with the potential for more prolonged therapy on an extension protocol thereafter). The severity of adverse events and laboratory abnormalities have been graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Pharmacokinetics have been obtained through 6 hours after dosing on Days 1 and 28 of idelalisib treatment. Pharmacodynamic assessment at baseline and during treatment have included evaluations of plasma chemokines and cytokines in all subjects and AKT activity in subjects with CLL. Antitumor activity has been assessed using standard criteria {Cheson 2007, Hallek 2008}. Response assessments have been performed after Cycles 1 and 2 and after every 2 cycles thereafter.

Study 101-02 has completed enrollment. A total of 191 subjects were enrolled to the study at dose levels of 50 mg BID (n=17), 150 mg QD (n = 16), 100 mg BID (n=25), 150 mg BID (n=45), 200 mg BID (n=35), 350 mg BID (n=17), and 300 mg QD (n=19). An additional cohort was also enrolled to receive IDELA 150 mg BID in 28 day cycles (21 days on IDELA/7 days off [n=17]). Patient characteristics were as follows: males/females n=139 (73%)/52 (27%) with median age of 64.5 [range 32-91] years. Diagnoses included: CLL, n=54 (28%); iNHL, n=64 (34%); aggressive NHL (MCL and DLBCL), n=49 (26%); AML, n=12 (6%);

and MM, n=12 (6%). Categorization of disease by response to the last prior therapy included: refractory, n=111 (58%); relapsed, n=79 (42%); and unknown, n=1 (1%). The median [range] number of prior therapies was 5 [1-14]. Among subjects with iNHL and CLL, the majority had received prior rituximab and prior alkylating agent therapy.

Adverse events were usually mild to moderate and not clearly idelalisib-related. Among Grade ≥3 adverse events, pneumonias and diarrhea were notable. Pneumonia was observed in 23 (12%) subjects, primarily in subjects with CLL. In most instances, these findings wereconsidered bacterial in origin, based either on culture results or on response to conventional antibiotics. Grade ≥3 adverse events of diarrhea were seen in 11 subjects (5.6%). Other Grade ≥3 events have included rash in 3 (1.6%) subjects. The relative contributions of disease-related factors, toxicity from prior therapies or ongoing supportive care, and idelalisib to these events was not clear.

Grade ≥3 hematological laboratory abnormalities included neutropenia, n=46 (24%); thrombocytopenia, n=27, (14%), anemia, n=14 (7.3%), and lymphopenia 13 (6.8%); with 12 subjects (6.3%) having febrile neutropenia. The occurrence of these events was greater in subjects with leukemia, particularly in those with pre-existing hematological abnormalities due to disease or prior therapy, commonly making attribution of these events to idelalisib uncertain.

Consistent with the observations in the 28-day dog toxicology study, reversible Grade ≥3 ALT/AST elevations occurred in 28 (15%) subjects and have been attributed to idelalisib. Onset generally occurred 2 to 16 weeks after idelalisib initiation and resolution was usually seen 2 to 6 weeks after idelalisib interruption. After resolution of ALT/AST changes, 14 subjects were rechallenged at the same or a reduced dose of idelalisib and 9 (64%) of these subjectswere able to resume treatment without recurrence of transaminase elevations. Two (1.0%) subjects had elevations in bilirubin, both of whom had confounding factors (recent history of biliary obstruction or concomitant use of potentially hepatotoxic medications) so that a causal relationship to idelalisib could not be established.

Pharmacokinetic analyses indicated that the increase in C_{max} and $AUC_{0\text{-}6h}$ with dose was less than dose-proportional, with modest increases above the dose level of 150 mg BID.

Pharmacodynamic data supported drug activity. In subjects with NHL, plasma concentrations of chemokines CCL22 and CCL17 were elevated at baseline and showed significant decreases within 1 cycle of idelalisib treatment ($p<0.001$ for both comparisons). Flow cytometry of CLL cells from subjects showed that idelalisib reduced constitutive expression of phosphorylated AKT to background levels when measured after 1 week of treatment ($p<0.0001$), demonstrating pharmacodynamic inhibition of activated PI3K signaling. Plasma concentrations of chemokines CCL3, CCL4, and CXCL13 were elevated in CLL subjects at baseline and decreased significantly within 1 cycle of idelalisib administration ($p<0.001$ for all comparisons).

Tumor reductions meeting antitumor response criteria were not observed in subjects with AML or MM. One of 11 subjects with DLBCL achieved a PR. In 104 subjects with iNHL and MCL, idelalisib induced PRs at all dose levels, with respective ORRs in enrolled subjects of 29/64 (45%) for iNHL and 16/40 (40%) for MCL. The median DOR was not been reached in subjects with iNHL; 19 subjects continued to receive idelalisb in a long-term extension study.

The median [range] DOR was 2.7 months [1 month to 8 months] in subjects with MCL; 6 MCL subjects contined to receive idelalisib in a long-term extension study.

In subjects with CLL, idelalisib reduced lymphadenopathy in almost all subjects; 44/54 (81.5%) achieved a lymph node response (≥50% reduction in target nodal lesions). An initial increase in peripheral absolute lymphocyte counts of >50% from baseline was observed some subjects; increases were maximal during the first 2 cycles and decreased thereafter; the pattern suggested drug-mediated lymphocyte redistribution. In 54 subjects with CLL, 39/54 (72%) achieved a PR (includes PR with lymphocytosis). The median DOR was not reached; 23 subjects continued to receive idelalisb in a long-term extension study.

2.6. Summary and Conclusions

Based on the collective data regarding the natural history of iNHL, current therapies for iNHL, and the nonclinical and clinical information regarding idelalisib, it is concluded that:

- iNHL is a serious, disabling, and potentially life-threatening disorder that requires sequential treatment with agents that provide alternative mechanisms of tumor control. Development of a therapy that can address disease pathogenesis with a new mechanism of action would address unmet medical need, particularly when applied in subjects with disease that is refractory to rituximab and alkylating agents.

- PI3Kδ over-expression plays an important role in iNHL biology. Further evaluation of idelalisib as a potential treatment for iNHL has sound scientific rationale founded on knowledge of its actions to selectively abrogate PI3Kδ activity and to inhibit lymphoma growth and survival in nonclinical models of lymphoid malignancy. These data are supported by clinical documentation of inhibition of PI3Kδ signaling in subjects with CLL participating in Phase 1 studies.

- The safety of advancing idelalisib into the proposed study is well supported by safety pharmacology and toxicology studies and by Phase 1 safety data obtained in healthy volunteers and subjects with lymphoid cancers.

- The potential for clinical efficacy of idelalisib in subjects with previously treated iNHL has been demonstrated in Phase 1 studies involving subjects with similar characteristics as are expected in this trial; these efficacy data in subjects with iNHL are supported by the observation of substantial antitumor activity in subjects with MCL and CLL.

- The dosing regimen planned for this study builds on dose-response and exposure-relationships observed in Phase 1 studies of idelalisib.

- Given the seriousness of iNHL and the aggregate potential benefits considered in the context of potential risks, further development of idelalisib in this Phase 2 clinical trial is justified.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

- To evaluate tumor regression as determined by ORR in subjects receiving idelalisib for treatment of iNHL refractory to rituximab and alkylating agents

3.2. Secondary Objectives

- To determine the onset, magnitude, and duration of tumor control and of treatment success in subjects receiving idelalisib
- To characterize HRQL as reported by subjects with iNHL receiving idelalisib
- To evaluate the effects of idelalisib on subject performance status
- To assess the pharmacodynamic effects of idelalisib
- To evaluate idelalisib treatment administration and compliance with idelalisib therapy
- To describe the safety profile of idelalisib
- To characterize idelalisib plasma exposure over time

PPD

3.3. Primary Endpoint

- ORR – defined as the proportion of subjects who achieve a confirmed complete response (CR) or partial response (PR; or MR for subjects with WM) during idelalisib treatment; response definitions will be based on standard criteria {Cheson 2007}

3.4. Secondary Endpoints

- DOR – defined as the interval from the first documentation of CR or PR (or minor response (MR) for subjects with WM) to the earlier of the first documentation of disease progression or death from any cause
- Lymph node response rate (LNR) – defined as the proportion of subjects who achieve a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes
- TTR – defined as the interval from the start of idelalisib treatment to the first documentation of CR or PR (or MR for subjects with WM)

- PFS – defined as the interval from the start of idelalisib treatment to the earlier of the first documentation of disease progression or death from any cause
- Overall Survival (OS) – defined as the interval from randomization to death from any cause
- Changes in HRQL as reported by subjects using the FACT-Lym (Appendix C)
- Changes in performance status as documented using the Karnofsky performance criteria (Appendix D)
- Changes in the plasma concentrations of disease-associated chemokines and cytokines
- Overall safety profile of idelalisib characterized by the type, frequency, severity, timing, and relationship to study therapy of any adverse events or abnormalities of physical findings, laboratory tests, or ECGs; drug discontinuations due to adverse events; or serious adverse events
- Study drug administration as assessed by prescribing records and compliance as assessed by quantification of used and unused drug
- Idelalisib trough and peak plasma concentrations assessed pre-dose and 1.5 hours post-dose

3.5. Rationale for Endpoint Selection

The proposed endpoints have been chosen based on relevance to the pathophysiology and clinical manifestations of iNHL, the known pharmacology of idelalisib, and the goals of the study in documenting idelalisib benefit:risk. All of the endpoints have been employed in prior studies in iNHL and can be evaluated with acceptable reliability and accuracy.

3.5.1. Antitumor Activity

Assessments of changes in tumor size using radiographic imaging techniques are routinely used in determining therapeutic effect and disease course in subjects with iNHL {Cheson 2007}. In addition, because subjects are being treated until tumor progression, repeated radiographic tumor assessment must be performed in order to define the proper duration of treatment for each study participant.

Characterization of ORR and changes in tumor size are necessary for confirming idelalisib drug effect and the potential for drug-related benefit. Lymphoma-related nodal enlargement is a major cause of subject discomfort and can cause organ dysfunction. Shrinking lymphadenopathy is an important therapeutic goal for improving subject well-being and relieving obstructive symptoms. Given that the natural history of iNHL is inexorable nodal growth, reductions in tumor extent during therapy provide strong evidence of idelalisib pharmacological activity. In addition, because of the association of lymph node size and subject symptoms, it can be inferred that

drug-mediated reductions in pathological nodal enlargement are reasonably likely to predict clinical benefit, thus meeting a regulatory standard for drug approval {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) 2007}.

Determinations of DOR and TTR are important in characterizing the rapidity of achieving tumor shrinkage and the duration of tumor control. PFS conveys longitudinal information regarding tumor control for both subjects who meet response criteria and those who do not. To ensure consistency of reporting relative to prior results, standard radiographic response and progression criteria {Cheson 2007} will be used to evaluate the ability of idelalisib to induce tumor shrinkage and extend tumor control. The timing of radiographic tumor assessments is consistent with the approach used in the recent registration-directed study of bendamustine in subjects with rituximab-refractory iNHL {Kahl 2010}. Evaluation of response and progression information by both investigators and the IRC will provide additional assurance regarding the accuracy of response assessments.

3.5.2. Changes in Health-Related Quality of Life

Direct patient reporting of outcomes using standardized methods has become an increasingly important component of therapeutic assessment. Evaluation of patient-reported outcomes (PROs) is particularly relevant in subjects who cannot be cured of disease {Reeve 2007}. PRO questionnaires have been previously used in iNHL to predict treatment outcome, to characterize the symptomatic effects of therapeutic tumor control, to assess subject perceptions of benefit and risk, and to assess outcomes in long-term survivors of lymphoma therapy {Crespi 2010, Mols 2007, Smith 2009, Webb 2010}.

In this study, it is postulated that idelalisib-mediated tumor control will be correlated with changes in HRQL and that assessments of the drug's safety profile will be supported by HRQL evaluations. The FACT-Lym (Appendix C) has been selected to evaluate such outcomes for the study. The FACT-Lym comprises a general HRQL measure for subjects receiving cancer treatment that yields a total score and subscales for physical, functional, social/family and emotional well-being {Cella 1993} and a diagnosis-specific measure for subjects with NHL {Cella 2005}. The FACT-Lym was developed to assess concerns (eg, nodal swelling, fevers, night sweats, weight loss, fatigue, infection) specifically relevant to lymphoma subjects. FACT instruments have documented psychometric properties {Brucker 2005, Cella 1993}, {Cella 2005, Victorson 2008} and have been shown to differentiate subjects with active NHL from those who are in disease remission {Smith 2009}.

The FACT-Lym instrument is available in appropriate languages for this study. FACT-Lym data will be obtained in at baseline and during each investigational clinic visit during treatment. Having FACT-Lym data concurrent with tumor response information will allow an evaluation of the potential relationship between tumor response and symptomatic changes as reported by subjects. To avoid biasing HRQL results, the FACT-Lym will be administered at each visit before other procedures are performed and before any study information is conveyed to the subject.

3.5.3. Changes in Performance Status

Performance status in subjects with iNHL is predictive of treatment outcome and provides an integrated assessment of subject well-being before, during, and after treatment {Lim 2008, Thieblemont 2008, Winkelmann 2011}. Ideally, performance status assessments may indicate how drug efficacy and toxicity affect subject functioning.

In this study, it is conjectured that idelalisib-mediated tumor control will be correlated with changes in performance status and that assessments of the drug's safety profile might be supported by performance status evaluations. The well-established, reliable, and validated Karnofsky performance score {Karnofsky 1949, Schag 1984, Yates 1980} (see Appendix D) will be employed in the trial for characterization of the subject population and repeated assessment of performance status.

3.5.4. Pharmacodynamic Activity

In lymphoma, disease-related perturbations in inflammatory status can be clinically overt; subjects often develop bothersome B symptoms (fevers, night sweats, and weight loss) that are characteristic of excessive systemic inflammation {Friedberg 2008b, Salles 2007}. Consistent with such disease manifestations, chemokines

and cytokines that are markers of aberrant B-cell trafficking or perturbations in inflammation are overexpressed by iNHL tissues and circulate in plasma; in Phase 1 studies it has been confirmed that plasma concentrations of such biomarkers are circulating in abnormally high quantities in subjects with iNHL and CLL {Furman 2010, Kahl 2010}. Thus, it is hypothesized that drug-mediated changes in these biomarkers provide direct evidence of mechanism-specific drug effects on PI3Kδ activity or indirectly document drug effects on overall tumor cell volume. In either case, improvements in these pharmacodynamic measures provide corroborative evidence in support of idelalisib pharmacological activity. In addition, it is possible that disease-or inflammation-related biomarkers may provide corollary information relating to the adverse lymphoma-specific effects of idelalisib on the liver; such data might allow better prediction of which subjects might be most susceptible to ALT/AST elevations during idelalisib treatment.

Based on these considerations, this study will evaluate circulating concentrations of relevant chemokines and cytokines with a particular focus on CCL7, CCL17, CCL22, CXCL12, CXCL13, interleukin-6, tumor necrosis factor-α, and C-reactive protein. In addition serum markers of iron metabolism (eg, hepcidin, iron, ferritin, transferrin) that that might provide markers linking lymphoma-related inflammation with perturbations of liver iron and sensitivity to liver injury will be evaluated {Ferrucci 2010, Nemeth 2003}. Appropriate methods for the measurement of circulating biomarkers have been determined. Clinically validated assays (eg, enzyme-linked immunosorbent assays [ELISAs]) will be used to measure circulating concentrations of chemokines and cytokines at baseline and during the course of idelalisib therapy.

3.5.5. Safety

In defining the therapeutic activity of a drug in a particular clinical setting, it is imperative that its safety profile be fully characterized. As is conventional in all clinical studies, proper description of each adverse event or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. In this study, particular focus will be placed on monitoring for adverse events and laboratory abnormalities that were encountered in the prior toxicology studies and clinical experience with idelalisib. Safety parameters of specific interest include those relating to infection, colitis, rash, liver injury, and bone marrow dysfunction. Particular scrutiny will be applied to adverse events causing interruption or discontinuation of idelalisib and to serious adverse events requiring rapid regulatory reporting.

In addition, the protocol will evaluate the potential for adverse effects of chronic idelalisib administration on normal lymphocyte number; the absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells will be assessed by flow cytometry. Serum concentrations of IgA, IgE, IgG, and IgM will be followed at baseline and during protocol therapy.

For consistency of interpretation, adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA), and the severity adverse events and laboratory abnormalities will be graded using the well-defined CTCAE, Version 3.0. Standard definitions for seriousness will be applied (see Section 8.2.1.2).

3.5.6. Study Drug Administration and Compliance

Evaluation of study drug administration and compliance provides context for assessments of safety, pharmacokinetics, and pharmacological activity. Evaluations of treatment administration and modifications from planned therapy document the influence of treatment-emergent adverse events on prescribing practice. Compliance assessment offers a general indication of subjects' acceptance of therapy, integrating factors of tolerability, palatability, and convenience.

In this study, information regarding planned treatment and modification from planned treatment (eg, dose reductions and interruptions) will be kept. The compliance of the subject will be verified by accounting for used and unused drug.

3.5.7. Pharmacokinetics

Given the intent of this protocol to assess longer-term dosing, collection of plasma for idelalisib concentrations is important for evaluating the steady-state maintenance of exposure over time. These data may allow correlations of exposure with measures of efficacy and toxicity. For this evaluation, limited plasma sampling will be performed every 4 weeks in all study subjects during the first 12 weeks of treatment. Based on existing clinical data, this 12-week duration of sampling provides acute and steady-state exposure information over a period in which antitumor activity and pharmacodynamic effects are evident and in which potential drug toxicity may occur. Samples will be collected pre-dose and 1.5 hours post-dose relative to the morning administration of idelalisib. This approach will provide information regarding trough plasma concentrations and will describe drug absorption as characterized by the approximate maximum concentration after the morning dose.

PPD

4. SUBJECT SELECTION

4.1. Subject Selection Criteria

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria is subject to review in the case of a Good Clinical Practice (GCP) or a regulatory authority audit. Any questions regarding a subject's eligibility should be discussed with the study sponsor medical expert prior to enrollment.

4.1.1. Inclusion Criteria

Subjects must meet all of the following conditions to be eligible for enrollment into the study:

1) Age ≥18 years.

2) Karnofsky performance score of ≥60 (Eastern Cooperative Oncology Group [ECOG] performance score of 0, 1, or 2) (see Appendix D).

3) Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to the following based on criteria established by the World Health Organization (WHO 2008 classification of tumors of haematopoietic and lymphoid tissues:

   - Follicular lymphoma (FL) Grade 1, 2, or 3a
   - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count < 5 x 10^9/L at the time of diagnosis and on baseline laboratory assessment performed within 4 weeks prior to the start of study drug administration
   - Lymphoplasmacytic lymphoma (LPL), with or without associated Waldenstroms Macroglobulinemia (WM)
   - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)

4) Histological materials documenting diagnosis of lymphoma available for review.
   Note: Central pathology confirmation of diagnosis will be performed in this study. However, a subject may be enrolled without waiting for confirmation of histological diagnosis on condition that pathological materials are known to be available for review.

5) Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or MRI).

6) Prior treatment with ≥2 prior chemotherapy- or immunotherapy-based regimens for iNHL.

7) Prior treatment with rituximab and with an alkylating agent (eg, bendamustine, cyclophosphamide, ifosfamide, chlorambucil, melphalan, busulfan, nitrosoureas) for iNHL.

8) Lymphoma that is refractory to rituximab and to an alkylating agent. Refractoriness is defined as:

   - Rituximab (without chemotherapy):

     — Lack of a CR or PR during rituximab therapy comprising ≥4 doses of ≥375 mg/m^2 given weekly, or

     — Occurrence of progressive disease (PD) within 6 months of the completion of a regimen of rituximab therapy comprising ≥4 doses of ≥375 mg/m^2 given weekly, or

     — Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy

   - Rituximab (with chemotherapy):

     — Lack of a CR or PR during rituximab-containing therapy comprising ≥2 doses of ≥375 mg/m^2, or

     — Occurrence of progressive disease (PD) within 6 months of the completion of a regimen of rituximab-containing therapy comprising ≥2 doses of ≥375 mg/m^2, or

     — Occurrence of PD during rituximab maintenance therapy or within 6 months of completion of rituximab maintenance therapy

   - Alkylating agent (administered with or without rituximab):

     — Lack of a CR or PR during alkylating-agent-containing therapy comprising ≥ 2 cycles of treatment, or

     — Occurrence of PD within 6 months of the completion of a regimen of alkylating-agent-containing chemotherapy comprising ≥2 cycles of treatment

   Note: Review of subject treatment records will be performed to ensure that subjects enrolled to the study meet the definition of rituximab- and alkylating-agent refractoriness that has been established for this trial.

9) Discontinuation of all other therapies (including radiotherapy or chemotherapy) for the treatment of iNHL ≥3 weeks before initiation of study treatment (Visit 2).

10) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤1 before initiation of study treatment (Visit 2) (with the exception of alopecia [Grade ≤2 permitted], neurotoxicity [Grade ≤2 permitted], or bone marrow parameters noted in Table 1 [Grade ≤2 permitted]).

11) Required baseline laboratory data (within 4 weeks prior to start of study drug administration) as shown in Table 1. ***Note: Confirmation should be performed for out-of-range values to determine if the abnormality is real or artifactual. Values used to establish eligibility should be obtained within the screening period, and should generally be the most recent measurement obtained.***

Table 1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Bone marrow	ANC	≥1.0 x 10^9/L
	Platelets	≥50 x 10^9/L
	Hemoglobin	≥80 g/L (8.0 g/dL or 4.9 mmol/L)
Hepatic	Serum total bilirubin	≤1.5 x ULN (unless elevated due to Gilbert's syndrome)
	Serum ALT	≤2.5 x ULN
	Serum AST	
Renal	Serum creatinine	<1.5 x ULN
Pregnancy	Serum β-HCG (for females of childbearing potential)	Negative
Infection	HIV	Negative antibody
	HBV	Negative HBsAg (if serology positive for infection)
	HCV	Negative viral RNA (if serology positive for infection)

Abbreviations: ANC, absolute neutrophil count; ULN, upper limit of normal ; ALT, alanine aminotransferase; AST, spartate aminotransferase; β-HCG, beta human chorionic gonadotropin; HIV , human immunodeficiency virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RNA, ribonucleic acid

12) For men and women of childbearing potential (ie, subjects who are not postmenopausal or surgically sterile), willingness to abstain from sexual intercourse or employ an effective method of contraception during the study drug administration and follow-up periods. ***Note: The definition of effective contraception will be based on the judgment of the investigator.***

13) Willingness and ability to provide written informed consent and to comply with scheduled visits, drug administration plan, imaging studies and contrast dye administration, laboratory tests, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.

14) Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation.

15) In the judgment of the investigator, participation in the protocol offers acceptable benefit:risk when considering current iNHL disease status, medical condition, and the potential benefits and risks of alternative treatments for iNHL.

4.1.2. Exclusion Criteria

The presence of any of the following conditions will exclude a subject from study enrollment:

1) Central nervous system or leptomeningeal lymphoma.

2) Known histological transformation from iNHL to diffuse large B-cell lymphoma.
Note: Biopsy documentation of the absence or presence of transformation is not required.

3) History of a non-lymphoma malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, localized prostate cancer, other adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥5 years.

4) Evidence of ongoing systemic bacterial, fungal, or viral infection (excluding viral upper respiratory tract infections) at the time of initiation of study treatment (Visit 2).
Note: Subjects with localized fungal infections of skin or nails are eligible. Subjects may be receiving prophylactic antiviral or antibacterial therapies at the discretion of the investigator. For subjects who are at substantial risk of an infection (eg, influenza) that may be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of protocol therapy.

5) Pregnancy or breastfeeding.

6) Ongoing alcohol or drug addiction.

7) Known history of drug-induced liver injury, chronic active HCV, chronic active HBV, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver or portal hypertension.

8) History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.

9) Ongoing immunosuppressive therapy, including systemic corticosteroids.
Note: Subjects may be using topical or inhaled corticosteroids.

10) Prior therapy with idelalisib

11) Exposure to another investigational drug within 3 weeks prior to start of study treatment.

12) Concurrent participation in another therapeutic treatment trial.

13) Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the subject; alter the absorption, distribution, metabolism or excretion of the study drug; or impair the assessment of study results.

4.2. Enrollment Criteria Rationale

The eligibility criteria are designed to limit enrollment to subjects who clearly have iNHL and who are sufficiently well to safely participate in study procedures and provide interpretable results. The requirement of measurable lymphadenopathy ensures that subjects have lymphoma that justifies therapy and can adequately be assessed for evidence of drug activity. Prior therapy provisions are intended to define a population that has already received available therapies with well-defined activity and is appropriate for inclusion in a study evaluating an investigational drug. Existing agents have shown activity in subjects who have disease resistant to either immunotherapeutic or chemotherapeutic agents, but not both. This study will evaluate idelalisib in a population of particular medical need, ie, those subjects whose disease has become refractory to both rituximab and alkylating agents. In delineating this population, definitions have been used that build on those employed in past studies {Kahl 2010, Witzig 2002}. Central reviews of lymphoma diagnosis and refractory status provide additional context for the validity of study results.

Subjects must not have serious prior or concomitant conditions or therapies that would compromise safety, compliance, or evaluation. Severe comorbid conditions (eg, hepatic dysfunction) may mask, exacerbate, or confound the interpretation of adverse effects of idelalisib and therefore subjects with such medical disorders are excluded. Pregnancy testing and restrictions on eligibility relating to reproductive potential, pregnancy, and breastfeeding are important because idelalisib is a new chemical entity and adverse effects relating to fertility, pregnancy, or drug transmission via breast milk are possible.

To minimize missing data and premature discontinuations, subjects should have sufficient psychological and social resources to comply with study procedures and restrictions. Consistent with GCP guidelines, subjects must provide informed consent before initiation of any study procedures.

5. ENROLLMENT AND STUDY MANAGEMENT PROCEDURES

5.1. Number of Subjects

The primary analysis will be based upon the intention-to-treat (ITT) principle. However, as many as 120 subjects may be enrolled in order to ensure enrollment of ≥100 subjects who have a documented diagnosis of lymphoma, who have confirmed refractory disease, and who can be evaluated for tumor response with baseline and on-study scans (ideally through the planned 24-week, follow-up tumor assessment). Thus, if an eligibility criterion or protocol violation occurs that substantially impairs evaluation of safety and activity in a study participant, or if a study participant does not undergo both a baseline and on-study tumor assessment, another subject can be enrolled to complete accrual of the planned number of evaluable subjects. The decision to accrue replacement subjects will be made by the study sponsor medical expert.

5.2. Subject Recruitment

Study candidates comprise subjects with iNHL who are being followed at the specified study sites or are referred to the study sites. Subjects will be enrolled from investigational sites in North America and Europe. The site principal investigator, designated sub-investigators, or other designees will discuss the possibility of participation directly with subjects who may be appropriate candidates for the study.

A description of the protocol will be posted on the ClinicalTrials.gov website.

5.3. Subject Compensation for Participation

For subjects requesting such assistance, reasonable reimbursements for the costs of travel required to participate in this study will be provided by the study sponsor. To receive payment for travel, subjects will need to submit the original travel receipts to the research study staff at the investigational site.

PPD

However, other than medical care that may be provided, subjects will not be paid for participation in the study. Payments for such items as lost wages, disability, discomfort due to injury, or meals obtained while waiting at the clinical research center will not be provided. Through the informed consent process, study candidates will be notified that their insurance company could be charged for standard care that is a component of this research study and that subjects may be responsible for co-payments and deductible payments that are typical for their insurance coverage.

5.4. Enrollment of Subjects Without Prior Treatment with Bendamustine

Given the increasing relevance of bendamustine as a component of treatment for subjects with iNHL {Friedberg 2008a, Kahl 2010, Robinson 2008}, the number of subjects that have not received prior bendamustine (given alone or in combination with other agents) will be limited to no more than 50 of the total enrolled.

5.5. Interactive Web Response System

An interactive web response system (IWRS) will be employed to manage screening, enrollment, dose modifications, off-treatment, and other activities during the conduct of the trial. The IWRS will use this information to maintain a central log documenting screening, to manage enrollment and dose modifications, to assess current inventories of study drug, and to initiate any necessary resupply of study drug. In addition, the IWRS will gate accrual of subjects without prior treatment with bendamustine (see Section 5.4).

6. TREATMENTS

6.1. Study Drug

6.1.1. Description

Idelalisib is manufactured according to current Good Manufacturing Practices (cGMP). The study drug is provided in tablets intended for oral administration. Each tablet contains 100 or 150 mg of the active study drug substance. Inactive excipients present in the formulation are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The 100 mg tablets are orange, and the 150 mg tablets are pink. The yellow coating contains yellow iron oxide, polyethylene glycol, talc, polyvinyl alcohol (PVA) and titanium dioxide. The orange coating contains FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, polyethylene glycol, talc, PVA and titanium dioxide. The pink coating contains red iron oxide, polyethylene glycol, talc, PVA and titanium oxide. Details regarding the shape, size and color of each tablet dosage form will be provided in the pharmacy manual for the study.

6.1.2. Packaging

Idelalisib will be packaged in bottles containing 60 or 64 tablets. A label will be affixed to each bottle and will contain the following information translated into the official language(s) of the countries in which the clinical trials will be conducted:

- Sponsor name and address
- Protocol identifier
- Description of contents, including dose strength and fill count
- Caution statement (includes “keep out of reach of children” statement)
- Storage conditions
- Manufacture date and retest date
- Lot number

6.1.3. Source

Idelalisib will be supplied free of charge by the study sponsor. The IWRS will provide the site staff with information regarding the study drug tablet strength to be dispensed to that subject and instructions for dosing. Any questions or concerns regarding study drug supply should be referred to the study sponsor clinical project manager.

6.1.4. Storage and Stability

Bottles containing tablets of idelalisib will be stored at controlled room temperature (15 to 30°C). While stability of tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures up to 40°C or down to -20°C (eg, during shipping) will not adversely affect the drug. Stability data at the start of study will support the use of the drug product for ≥12 months. The clinical site will be updated as more stability data become available.

6.1.5. Dispensing

The clinic pharmacist or an alternative qualified person will be responsible for dispensing study medication. It is planned that drug will be dispensed at 4-week intervals through the first 24 weeks of treatment and at 12-week intervals thereafter. A modest overage will be supplied such that subjects have sufficient drug in case of loss, spillage, or necessary deviations in scheduling clinic returns (eg, due to inclement weather, holidays, etc). Tablets should be kept in the original bottles provided.

6.1.6. Return

Subjects should return all unused study medication to the study site at each applicable study visit.

6.1.7. Accountability

The disposition all idelalisib study drug should be documented from the time of receipt at the site through subject dispensing and return.

Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics, or allow the study drug to be used other than as directed by this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by the study sponsor or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed and the date, quantity and lot number of the study drug dispensed.

The study drug supply should be retrieved from subjects at the end of each dosing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. All returned study drug should be retained for review by the study site monitor prior to destruction.

Depending upon the decision of the study sponsor, remaining unused study drug supply will be returned to the study sponsor or its designee after the study is completed or will be discarded or destroyed at the clinical site. If the study drug is discarded or destroyed at the clinical site,

standard institutional policy should be followed. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

6.1.8. Overdose Precautions

For this protocol, an overdose is defined as administration of >700 mg of idelalisib in a single day. In a subject who experiences an overdose of this magnitude, idelalisib administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

The study sponsor medical expert should be contacted if an overdose occurs. Under applicable regulations, overdosing may result in a serious adverse event and may require reporting accordingly (see Sections 8.2.1.2 and 8.2.8).

6.1.9. Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, idelalisib does not appear to be acutely toxic, genotoxic, or irritative at levels that are likely to result from inadvertent exposure to the contents of broken capsules or tablets. Personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the study drug product. For further information regarding inadvertent exposure and spill precautions, please consult the idelalisib investigator brochure.

6.2. Study Drug Administration

6.2.1. Dosing Instructions

The prescribed dose of idelalisib should be taken orally. At each dose administration, the tablet number corresponding to the appropriate dose of idelalisib is to be swallowed whole with 100 to 200 mL (~ 4 to 8 ounces) of water. Subjects should be instructed not to bite or chew on the tablets. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.

Idelalisib may be taken with or without food. There are no known dietary restrictions related to idelalisib use. No specific premedications or supporting medications are required in conjunction with idelalisib administration.

6.2.2. Dosing Schedule

Idelalisib will be taken on BID schedule at approximately the same times each day. Ideally doses should be taken at ~12-hour intervals (eg, at ~7 AM and at ~7 PM). While it is realized that variations in dosing schedule may occur in the outsubject setting, the prescribed regimen (12-hour dosing intervals) should be followed as closely as possible, especially in the clinic.

At specified clinic visits, the study drug will be administered in the clinic with dosing appropriately timed relative to blood sampling for idelalisib pharmacokinetics. As detailed in Section 7.2, clinic staff should record peri-dosing food intake and idelalisib administration information, including the exact clock time of each dose, for doses of study drug administered in the clinic or hospital. Thereafter, subjects will be given an adequate supply of tablets to take at home.

6.2.3. Dose Levels

Idelalisib dose levels and tablet numbers are shown in Table 2 below. The starting dose level will be 150 mg BID. Lower dose levels are provided in case a subject requires idelalisib dose reduction.

Table 2. Idelalisib Dose Level Information

Dose Level	Dosing Regimen	Tablet Strength	Tablet Number Per Dose
Starting	150 mg BID	150 mg	1
-1	100 mg BID	100 mg	1

Abbreviation: BID, 2 times per day

Subjects should be followed closely for adverse events or laboratory abnormalities that might indicate idelalisib-related toxicity. Recommendations for idelalisib dose modification are provided in Section 6.2.4. If a subject experiences an idelalisib-related adverse event requiring dose modification during the course of idelalisib therapy, then study drug administration should be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree. Thereafter, idelalisib may be reinstituted, but the dose of idelalisib should be reduced by 1 dose level; successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate idelalisib at Dose Level -1 (100 mg BID) then the subject should be discontinued from study drug therapy.

After a dose is reduced, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of idelalisib for $\geq$ 4 weeks then the idelalisib dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not study drug-related. Successive adjustments to progressively higher dose levels can be made at 4-week intervals. The starting dose level (150 mg BID) should not be exceeded.

6.2.4. Safety Monitoring and Recommendations for Dose Modification

Subjects must be monitored closely for adverse events or laboratory abnormalities during the course of the study. Reference should be made to the CTCAE, Version 3.0 for grading the severity of adverse events and laboratory abnormalities (refer to http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

Based on Phase 1 clinical experience with idelalisib adverse events potentially attributable to idelalisib have included rash, colitis/diarrhea, pneumonitis, and hepatic laboratory abnormalities. While myelosuppression is not a prominent toxicity of idelalisib in previous experience, dose modification provisions for subjects experiencing neutropenia or thrombocytopenia are provided as a precaution. Recommendations for dose modification based on the type and severity of adverse events or laboratory abnormalities are provided in Table 3 and suggestions for evaluation and management of specific adverse events are also noted thereafter. Whenever possible, any dose adjustment of idelalisib should be discussed between the investigator and the study sponsor medical expert prior to implementation.

Table 3. Recommended and Required Actions Based on Type and Severity of Adverse Event or Laboratory Abnormality

	Recommendation
NCI CTCAE Grade	**Idelalisib**
HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤2 neutropenia	Maintain current dose level and schedule.
Grade 3 neutropenia	Maintain current dose level and schedule. **Required:** Monitor blood counts at least weekly until ANC Grade ≤2.
Grade 4 neutropenia (or occurrence of neutropenic fever or infection)	**Required:** Interrupt idelalisib dosing. Monitor blood counts at least weekly until ANC Grade ≤2. May resume idelalisib at lower dose when ANC is ≤ Grade 3.
Thrombocytopenia	
Grade ≤3	Maintain current dose level and schedule.
Grade 4	**Required:** Withhold idelalisib for bruising or bleeding until Grade ≤3. May resume idelalisib at initial or lower dose level at investigator discretion.
NON-HEMATOLOGICAL ADVERSE EVENTS	
Rash	
Grade ≤1	Maintain current dose level and schedule.
Grade 2	Maintain current dose level and schedule.
Grade ≥3	**Required:** Withhold idelalisib until Grade ≤1. May resume at lower dose level or discontinue idelalisib at investigator discretion.
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	
Any Grade	**Required:** Discontinue idelalisib. Institute systemic immunosuppression per institutional standards.

NCI CTCAE Grade	Recommendation Idelalisib
Gastrointestinal Inflammation/Diarrhea/Colitis	
Any Grade	Provide anti-diarrheal agent (eg, loperamide), ensure good hydration status and maintain current idelalisib dose level and schedule. **Required:** Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents. Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).
Grade 2	Provide anti-diarrheal agent (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). Ensure good hydration status and maintain current idelalisib dose level and schedule.
Grade ≥3 (or persistent Grade 2 without clear etiology)	Provide anti-diarrheal agent (eg, loperamide). Consider addition of anti-inflammatory agent (eg, sulfasalazine, budesonide). **Required:** Withhold idelalisib until Grade ≤1 Resume at lower dose level or discontinue idelalisib at investigator discretion.
Hepatic Adverse Events (elevations in ALT, AST, or bilirubin)	
Grade ≤1 (ALT/AST≤3xULN) (Bilirubin≤1.5xULN)	Maintain current dose level and schedule.
Grade 2 (ALT/AST>3-≤5xULN) (Bilirubin>1.5-≤3xULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per week.
Grade 3 (ALT/AST>5-≤20xULN) (Bilirubin>3-≤10xULN)	Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <3, resume idelalisib at same dose level. If bilirubin abnormality was Grade ≥3, resume at lower dose level.
Grade 4 (ALT/AST>20xULN) (Bilirubin>10xULN)	**Required:** Withhold idelalisib. Monitor ALT, AST, ALP, and bilirubin at least 1x per week until all abnormalities are Grade ≤1. If bilirubin abnormality was Grade <4, resume idelalisib at lower dose level. If bilirubin abnormality was Grade 4, discontinue idelalisib.
Pneumonitis *(with new onset or worsening of baseline dyspnea, cough or hypoxia without obvious infectious cause)*	
Grade 1 (asymptomatic)	**Required:** Withhold idelalisib until resolution to baseline. May resume at lower dose level or discontinue at investigator discretion.
Grade ≥ 2	**Required:** Discontinue idelalisib permanently in subjects with any severity of symptomatic pneumonitis and institute therapy as clinically appropriate.
Pneumocystis jirovecii pneumonia (PJP)	
Any Grade	**Required:** Discontinue idelalisib
Organizing Pneumonia	
Any Grade	Required: Discontinue idelalisib permanently.

NCI CTCAE Grade	Recommendation Idelalisib
CMV infection/Reactivation[a]	
Any Grade	**Required:** Interrupt idelalisib upon unequivocal clinical or laboratory evidence of CMV infection and initiate treatment according to established clinical guidelines. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.
Other Nonhematological Adverse Events	
Grade ≤2	Maintain current dose level and schedule.
Grade ≥3	Withhold idelalisib until Grade ≤1. Resume idelalisib at initial or lower dose level or discontinue idelalisib at investigator discretion.

a CMV should be diagnosed using clinical or laboratory criteria per established institutional standard
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST= aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, G-CSF=granulocyte colony-stimulating factor, NCI=National Cancer Institute, ULN=upper limit of normal

When there is a dose modification, the IWRS should be notified. In addition, the subject should be notified of the change in dose and the appropriate clinic staff should instruct the subject about the revised number of study medication tablets to be used per dose according to the new dose level. Any questions regarding dose modification should be referred to the study sponsor medical expert.

6.2.5. Management of Specific Adverse Events

6.2.5.1. Dermatological Events

Subjects receiving idelalisib with ≥ Grade 3 rash have generally presented with a maculopapular rash on the trunk and extremities that is occasionally associated with fever and/or pruritus and responded to treatment with diphenhydramine and/or topical or oral corticosteroids.

For subjects who develop a severe rash for which an underlying etiology cannot be identified (e.g., infection, co-suspect drug), study drug should be interrupted. Resumption of study drug should be considered once rash resolves.

Severe cutaneous reactions, including fatal events of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in subjects receiving idelalisib. Assessment of potential causal association between idelalisib and the occurrence of SJS or TEN has been confounded by the coadministration of antineoplastic agents (e.g., bendamustine, rituximab) and/or other concomitant medications known to be associated with SJS or TEN (e.g., allopurinol). If SJS or TEN is suspected, idelalisib and all coadministered medications associated with SJS or TEN should be interrupted and the subject treated accordingly.

Subjects should be monitored for the development of SJS, TEN, or other severe cutaneous reactions and idelalisib treatment should be discontinued if such events occur.

6.2.5.2. Gastrointestinal Events

Isolated cases of gastrointestinal inflammation (eg, stomatitis, colitis, cecitis) have been noted in subjects receiving idelalisib. Rare cases of gastrointestinal perforation have occurred, generally in the setting of occult carcinoma, mesenteric embolus or diverticular disease. Discontinuation of idelalisib is required in subjects who experience bowel perforation.

Cholangitis manifest as hyperbilirubinemia out of proportion to serum transaminase elevations has been observed. While disease-related factors, neutropenia, toxicity from prior therapies, effects of ongoing supportive care, or pre-existing cholelithiasis may have initiated such events, it is possible that idelalisib played a contributory role. In such subjects, rechallenge with idelalisib has been possible and has not been associated with other severe adverse events. Subjects who have developed evidence of enteritis during idelalisib therapy have been successfully treated with antidiarrheals (eg, loperamide) and with enteric steroidal (eg, budesonide) or non-steroidal (eg sulfasalazine [Azulfidine®]) anti-inflammatory agents and have been able to continue or resume idelalisib.

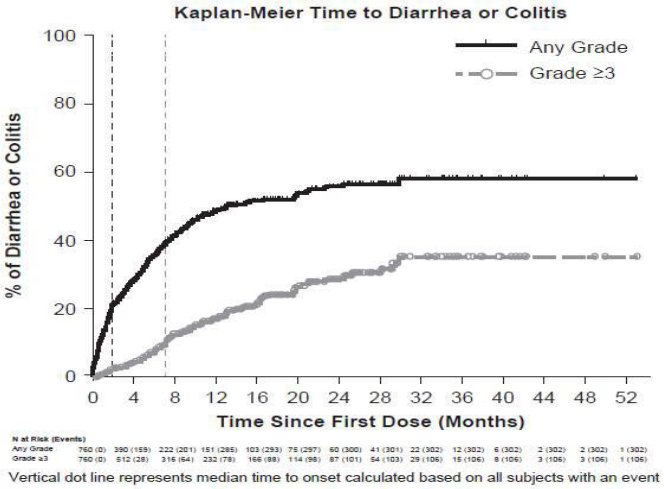
For study subjects who develop severe abdominal pain the possibility of a bowel obstruction or perforation should be considered. Appropriate clinical and radiographic examination should be performed and supportive care or surgical intervention should be considered.

For subjects who develop persistent diarrhea, causes related to concomitant medications or gastrointestinal infections such as Clostridium difficile (particularly for patients recently treated with broad spectrum antibiotics), Shigella, Campylobacter, Yersinia and CMV should be considered and treated if appropriate. Depending upon the clinical circumstances, endoscopy and biopsy, with bacterial and viral IHC staining should be considered. In the event that an infectious cause is not identified, an antimotility agent (eg, loperamide) may lessen symptoms and intervention with enteric steroidal (eg, budesonide) or non-steroidal (eg, sulfasalazine) anti-inflammatory agents should be considered. In such subjects, rechallenge with idelalisib at a lower dose level has resulted in recurrence of symptoms in some but not all subjects and has not been associated with other severe adverse events.

6.2.5.2.1. Investigation for Idelalisib Late Onset or Severe Diarrhea/Colitis

Among idelalisib-treated patients who reported diarrhea or colitis, the median time to onset of any grade diarrhea or colitis was 1.9 months (range, 0.0–29.8), of grade 1 or 2 was 1.5 months (range, 0.0–15.2) and of grade 3 or 4 was 7.1 months (range, 0.5–29.8). Kaplan–Meier curves of time to onset of diarrhea or colitis are shown for all idelalisib-treated patients in Figure 1 {Coutre 2015}.

Figure 1. Kaplan-Meier Time to Diarrhea or Colitis



Idelalisib-associated severe diarrhea responds poorly to antimotility agents however, median time to resolution ranged between 1 week and 1 month across trials following interruption of idelalisib treatment and, in some instances, initiation of corticosteroid treatment {Gilead Sciences Inc 2014}.

6.2.5.2.2. Evaluation for Gastrointestinal Events/Colitis

For Grade 2 colitis and diarrhea (unless clinical diagnosis is established from medical history and physical examination), the following testing is required:

- Stool culture for routine pathogens (Salmonella, Shigella, Campylobacter species, Clostridium difficile toxin, Rotavirus, Cytomegalovirus, Adenovirus)
- Stool for Ova and Parasites (Cryptosporidium parvum, Isospora belli, Enterocytozoon bieneusi, Septata intestinalis, Strongyloides, Microsporidia, Entamoeba histolytica, Cyclospora), Giardia antigen
- For grade ≥ 3 or persistent grade 2 colitis or diarrhea without clear etiology (eg, clostridium difficile enterocolitis), endoscopy with biopsy is required. All biopsy samples should include immunohistochemistry (IHC) and PCR for CMV, Adenovirus.

PPD

6.2.5.2.3. Differentiation Between Small-Bowel and Large-Bowel Diarrhea

Differentiation between small-bowel and large-bowel diarrhea: may be possible on a clinical basis. If unclear, consider upper and lower tract endoscopy with biopsy.

- Small bowel diarrhea is characterized by large volume diarrhea (more than one per day), possible associated dehydration weight loss and paraumbilical pain. Consider an endoscopic small-bowel biopsy and evaluate other etiologies such as celiac disease.

- Large-bowel diarrhea may present with lower pelvic pain, tenesmus, generally smaller stool volume with gross blood frquently found in the stool. Condsider a colonoscopic evaluation and biopsy.

6.2.5.3. Hepatic Events

Transaminase Elevations: Consistent with observations in a dog toxicology study, reversible asymptomatic ALT/AST increases were also observed early in the idelalisib program in phase 1 studies (101-02 and 101-07) in subjects with hematologic malignancies. Transaminase elevations generally occurred within 4 to 12 weeks of drug initiation, and resolved spontaneously over a period of 2 to 4 weeks with drug being continued for Grade 1 and 2 elevations and drug withheld for Grade 3 or 4 elevations until resolution. These early observations have been consistent with the ongoing experience with idelalisib treatment and transaminase elevations are now well characterized as most frequently asymptomatic, transient and occurring within the first 3 months of treatment.

Grade 1 or 2 elevations commonly resolve despite continued idelalisib treatment and Grade 3 or 4 elevations can be managed by temporarily withholding idelalisib. Successful rechallenge after resolution at either the same or lower dose level of idelalisib has been achieved in the majority of subjects. There has been no evidence of impaired synthetic function. Close monitoring of hepatic laboratory tests during therapy is important to allow for appropriate idelalisib interruption and reinstitution so that subjects may continue with study drug treatment.

6.2.5.4. Pulmonary Events

Documented bacterial, fungal, viral, and pneumocystis pneumonias have been observed in patients receiving idelalisib, primarily in patients with CLL. Some study subjects receiving idelalisib alone or in combination have developed evidence of pneumonitis and organizing pneumonia, respectively, without documented pulmonary infection.

Given the potential for infectious or drug-related adverse events, clinicians should be particularly observant for evidence of respiratory events in subjects participating in this trial. Subjects should be evaluated who describe pulmonary symptoms (eg, dyspnea on exertion, cough, shortness of breath); manifest a decline from baseline of ≥5% in oxygen saturation, or demonstrate evidence of pulmonary inflammation (eg, focal or diffuse interstitial pattern or ground-glass opacities on chest CT). Potential bacterial, fungal, or viral etiologies should be assessed. Noninfectious etiologies such as pulmonary edema or thromboembolism should also be considered.

As appropriate for the clinical situation and culture results, subjects should be treated empirically or given specific antibiotics, antifungals, or antiviral agents for a cultured organism. Supportive care, including oxygen or mechanical ventilation, should be provided as necessary.

For subjects with suspected Grade 1 pneumonitis, withhold idelalisib until resolution to baseline. Upon resolution to baseline, idelalisib may be resumed at a lower dose level or discontinued at investigator discretion. For subjects with Grade ≥2 pneumonitis (eg, new onset or worsening of baseline cough, dyspenea, hypoxia and/or a diffuse interstitial pattern or ground-glass opacities on chest imaging without obvious infectious etiology), idelalisib must be discontinued permanently and therapy initiated as clinically appropriate.

Cases of organizing pneumonia, some with fatal outcome, have occurred with idelalisib. In subjects presenting with serious lung events, idelalisib should be interrupted and the subject assessed for an explanatory etiology. If organizing pneumonia is diagnosed, treatment with idelalisib should be permanently discontinued and the subject treated accordingly.

6.2.5.5. Pregnancy, Lactation, and Reproduction

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. However, definitive reproductive toxicology studies in animals have not yet been performed and the specific effects of idelalisib on human embryogenesis or fetal development are unknown. Whether idelalisib is excreted in human breast milk is unknown. General toxicology studies of idelalisib in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The implications of these testicular changes for animal or human fertility are unknown.

Given the potential risks to a fetus or infant as a result of exposure to idelalisib, women of reproductive potential entering this study must have a negative serum pregnancy test at baseline and must not be breastfeeding. Males and females of childbearing potential should abstain from sexual intercourse or use an effective form of contraception during the course of the study and for 90 days following the last dose of study drug. If a female study participant becomes pregnant or decides to breastfeed during the course of the study, all study therapy must be discontinued.

PJP Prophylaxis

Trimethoprim sulfamethoxazole is rated a Pregnancy category C agent. In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects manifested mainly as cleft palates. One survey found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter. Because sulfamethoxazole and trimethoprim may interfere with folic acid metabolism it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapsone is rated a Pregnancy Category C agent. Extensive, but uncontrolled experience and two published surveys on the use of Dapsone in pregnant women have not shown that Dapsone increases the risk of fetal abnormalities if administered during all trimesters of pregnancy or can affect reproduction capacity. Because of the lack of animal studies or controlled human experience, Dapsone should be given to a pregnant woman only if clearly needed. Dapsone is excreted in breast milk in substantial amounts. Hemolytic reactions can occur in neonates. Because of the potential for tumorgenicity shown for Dapsone in animal studies a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of drug to the mother.

Atovaquone is rated a Pregnancy Category C agent. Atovaquone is teratogenic and did not cause reproductive toxicity in rats at plasma concentrations up to 2 to 3 times the estimated human exposure. Atovaquone can cause maternal toxicity in rabbits at plasma concentrations that were approximately one half the estimated human exposure. Mean fetal body lengths and weights were decreased and there were higher numbers of early resorption and post-implantation loss per dam. It is not clear whether these effects are caused by atovaquone directly or are secondary to maternal toxicity. Concentrations of atovaquone in rabbit fetuses averaged 30% of the concurrent maternal plasma concentrations. There are no adequate and well-controlled studies in pregnant women. Atovaquone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether atovaquone is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when Atovaquone is administered to a nursing woman. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma.

Aerosolized Pentamidine (NebuPent) is a Pregnancy Category C agent. There are no adequate and well controlled studies of NebuPent in pregnant women. One literature report indicated that intravenously administered pentamidine in pregnant rats at 4 mg/kg/day was embryolethal; teratogenicity was not observed in this study. It is unknown whether pentamidine administered via the aerosolized route crosses the placenta at clinically significant concentrations. It is not known whether NebuPent can cause fetal harm when administered to a pregnant woman. NebuPent should be given to a pregnant woman only if clearly needed. It is not known whether NebuPent is excreted in human milk. NebuPent should not be given to a nursing mother unless the potential benefits are judged to outweigh the unknown risks.

6.2.6. Hematological and Immunological Events

In the Phase 1 experience with idelalisib in patients with NHL and CLL, subjects with Grade ≥3 neutropenia, anemia, and/or thrombocytopenia were enrolled to clinical trials. Decreased levels of neutrophil counts, hemoglobin, or platelet counts during idelalisib administration were largely due to minor fluctuations in these parameters among subjects with pre-existing hematological abnormalities due to disease or prior therapy. Thus, idelalisib did not appear to induce overt myelosuppression. Obvious patterns of drug-mediated reductions in circulating CD4+ lymphocyte counts or suppression of serum IgG levels were also not observed.

Treatment-emergent Grade 3 or 4 neutropenia events including those accompanied by fever or infection have occurred in subjects treated with idelalisib, most commonly in the context of myelosuppressive agents such as bendamustine. For subjects who develop ANC 0.5 to < 1.0 Gi/L, blood counts should be monitored at least weekly. For subjects who develop ANC < 0.5 Gi/L, idelalisib should be interrupted and blood counts monitored at least weekly until ANC is ≥ 0.5 Gi/L, at which point, idelalisib dosing may be resumed at 100 mg BID. Management of neutropenia, including administration of G-CSF should be per established clinical guidelines and institutional standard of care.

6.2.7. Infectious Events

Patients with lymphoid cancers receiving idelalisib have developed serious and fatal infections during therapy. Opportunistic infections, most notably *Pneumocystis jirovecii* pneumonia (PJP) and CMV infection, have most frequently occurred within the first 6 months of treatment with idelalisib and are increased in the context of concurrent myelosuppressive therapy such as bendamustine.

Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment. Prophylaxis will continue for a period of 2 to 6 months after idelalisib discontinuation. The duration of prophylaxis should be based on clinical judgment and may take into account risk factors such as concomitant corticosteroid treatment and prolonged neutropenia after idelalisib treatment ends. Subjects must permanently discontinue idelalisib upon diagnosis of PJP.

CMV surveillance for active disease (quantitative PCR or PP65 antigen) must be conducted approximately every 4 weeks throughout the course of idelalisib treatment. CMV viral load testing should be performed from the same specimen type whenever possible and caution should be exercised when comparing CMV viral load results across different testing centers. If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must interrupt idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines. If the benefits of resuming idelalisib are judged to outweigh the risks, consideration should be given to administering pre-emptive CMV therapy.

In high-risk subjects (history of recurrent infection, allogeneic transplant, treatment with alemtuzumab, hypogammaglobulinemia) other infection prophylaxis should be considered per consensus guidelines. Administration of intravenous immunoglobulin is permitted per standard institutional practice {Raanani 2009}. For subjects who develop an infection, appropriate medical therapy should be instituted in a timely manner.

6.2.8. Secondary Malignancies

Subjects receiving idelalisib for CLL or iNHL have developed pre-malignant and secondary malignant diseases, such as basal cell carcinoma, myelodysplastic syndrome, myeloproliferative disorders, and more aggressive lymphoid malignancies (eg, have had Richter transformation). Generally this has occurred in subjects who have received multiple previous lines of therapy and when idelalisib is combined with other therapies such as rituximab or bendamustine. The specific association of the therapeutic agents with these types of events has not been determined.

There are reports of pre-malignant and malignant diseases that have developed in subjects who have been treated with bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. The specific association of the therapeutic agents with these types of events has not been determined.

6.2.9. Ultraviolet Exposure

In vitro studies indicate enhanced cytotoxicity when embryonic murine fibroblasts treated with GS-563117 (the major metabolite of idelalisib) are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern. Although specific clinical correlates for these nonclinical data are not available, investigators and study subjects should be observant for the possibility that study participants may have exaggerated sunburn reactions (eg, burning, erythema, exudation, vesicles, blistering, edema) involving areas of skin exposed to ultraviolet light.

6.2.10. Further Safety Information

Further safety information regarding the study drug may be found in the investigator brochure for idelalisib.

6.2.11. Duration of Therapy

Subjects may continue receiving idelalisib until the occurrence of any events requiring treatment discontinuation as defined in Section 9.

6.3. Concomitant and Supportive Therapy

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study of idelalisib.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use should be recorded on the case report forms (CRFs).

Information regarding use or restrictions on specific concomitant medications, dietary measures, or other interventions is provided below.

6.3.1. Anticancer or Experimental Therapies Other than Idelalisib

No other anticancer therapies (including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving study treatment with idelalisib. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

6.3.2. Antiemetics

Nausea and/or vomiting have not been commonly observed with idelalisib in prior studies. However, subjects who experience nausea or vomiting while on study therapy may receive antiemetics based on the judgment of the treating physician and local institutional practices. At the occurrence of persistent nausea or vomiting of severity grade ≥ 1, it is suggested that the subject receive an oral or transdermal serotonin antagonist (eg, dolasetron, granisetron, ondansetron, tropisetron, palonosetron). Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. If possible, systemic corticosteroids should be avoided (see Section 6.3.4).

6.3.3. Granulocyte Colony-Stimulating Factors and Erythropoietin

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms. Granulocyte colony-stimulating factor (G-CSF) agents and erythropoietic agents (eg, erythropoietin or darbepoetin) may be administered per institutional standard. Such use should be particularly considered if providing hematopoietic support might help to maintain idelalisib therapy. Reference should be made to the American Society of Clinical Oncology guidelines {Rizzo 2008, Smith 2006}.

6.3.4. Corticosteroids

Subjects may receive topical or inhaled corticosteroids while on study. The use of systemic corticosteroids is discouraged because their potential antineoplastic activity in subjects with iNHL may confound interpretation of idelalisib-mediated antitumor effects. However, subjects who develop severe or life-threatening conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

6.3.5. Drugs that Inhibit/Induce CYP3A-Dependent Metabolism

Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and cytochrome P450 3A (CYP3A). Idelalisib also undergoes minor metabolism by UDP-glucoronosyltransferase 1-4 (UGT1A4). The AUC of idelalisib was increased 1.8-fold when idelalisib was coadministered with a strong CYP3A inhibitor. Therefore, if subjects are taking concomitant strong CYP3A inhibitors, the subject should be monitored closely for signs of idelalisib toxicity and the dose modifications for adverse reactions should be followed in the event of toxicity (see Table 3).

Additionally, idelalisib exposures are approximately 75% lower when coadministered with rifampin, a highly potent inducer of CYP3A. Therefore, avoid coadministration of strong inducers of CYP3A (rifampin, carbamazepine, phenytoin, and St. John's wort) with idelalisib.

6.3.6. Drugs that Undergo CYP3A-Dependent Metabolism

The metabolite of idelaisib, GS-563117, is a reversible and time-dependent inhibitor of CYP3A; accordingly coadministration of idelalisib with midazolam, a probe CYP3A substrate, resulted in a ~5-fold increase in midazolam systemic exposure (AUC), indicating that idelalisib is a strong inhibitor of CYP3A. Coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, antiarrhythmics, calcium channel blockers, benzodiazepines, certain HMG-CoA reductase inhibitors, phosphodiesterase-5 (PDE5) inhibitors, warfarin). Avoid coadministration of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, terfenadine) with idelalisib.

6.3.7. Immunization

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals (see Section 2.4.3.2). The specific clinical relevance of these nonclinical findings is unknown. However, for subjects who are at substantial risk of an infection (eg, influenza) that may be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of treatment with idelalisib.

6.3.8. Surgery

There are no known effects of idelalisib on coagulation or wound healing. Pending receipt of additional information, idelalisib may be continued in the peri-procedural period in subjects who require surgery or invasive procedures.

6.3.9. Diet

There are no specific dietary restrictions in the study. Idelalisib may be taken with or without food.

6.4. Study Treatment Rationale

Selection of the idelalisib treatment regimen (including starting dose level, dose-modification levels, schedule, duration, and conditions of administration) for this study has been based on primarily on safety, exposure and activity profiles from previous Phase 1 clinical studies involving healthy volunteers, subjects with allergic rhinitis, and subjects with refractory/relapsed lymphoid malignancies. The following information was considered:

- Idelalisib was symptomatically well tolerated in subjects with lymphoid malignancies receiving dose levels of 50 mg BID through 350 mg BID (the highest dose level tested). Monitorable, reversible transaminase elevations were observed in some subjects with iNHL but dose-dependency could not be clearly established and no MTD was apparent over this dose range.

- Increases in idelalisib plasma C_{max}, AUC, and C_{trough} values were less than dose-proportional in subjects with lymphoid malignancies; the dose-exposure evaluation indicated modest increases in plasma exposure at dose levels >150 mg BID. Thus, administration of idelalisib doses higher than 150 mg BID does not appear warranted given that no attendant gains in exposure would be expected. In Phase 1 studies, the mean plasma $t_{1/2}$ of idelalisib was ~6.5 to 9.8 hours across dose levels.

- In an allergic rhinitis study, idelalisib induced statistically significant improvements in clinical and pharmacodynamic endpoints when administered at 100 mg BID over 7 days. These data support the pharmacological relevance of idelalisib-mediated PI3Kδ inhibition when administered at a dose-level approximating that to be used in this Phase 2 study.

- A positive correlation was noted between idelalisib dose and improvement in lymphadenopathy in subjects with B-cell malignancies, with near-maximal effect was apparent at 150 mg BID. Thus, treatment with a idelalisib dose of 150 mg BID is considered appropriate.

- The idelalisib dose modification provisions described in the protocol are designed to balance a primary concern for subject safety with the potential for observing pharmacological and antitumor activity in circumstances under which a subject experiencing an adverse event may still be able to continue on therapy at a lower idelalisib dose level. The enhanced monitoring to be performed and the actions to be taken in response to toxicity are based on experience with interruption, dose-modification, rechallenge, and re-escalation already piloted in idelalisib Phase 1 trials. In addition, idelalisib antitumor activity has been observed in the Phase 1 studies across all dose levels tested, including doses in the range of the modified Dose Levels -1 (100 mg BID) planned for this protocol. Thus, use of these lower dose levels to accommodate individual subject tolerability in this protocol is justified because subjects receiving such idelalisib dose levels still have the potential for benefit.

- Treatment until the occurrence of disease progression or unacceptable toxicity is appropriate to obtain information regarding drug safety during chronic administration. Prolonged therapy also offers study participants the potential for maximum benefit from treatment.

- The changes in exposure observed when administering idelalisib after a high-fat, high-calorie meal are modest (~40% increase in mean AUC with no change in mean C_{max}). Thus, idelalisib can be administered with or without food.

- Overdose is defined as administration of >700 mg of idelalisib in a single day because this dose is >2 times the planned starting dose of 150 mg BID and exceeds the maximum administered dose of 350 mg BID that has been shown to be generally well tolerated in the existing Phase 1 experience.

7. SCHEDULE OF EVENTS AND PROCEDURES

7.1. Schedule of Events

An overview of the proposed procedures and types and timing of data to be collected and recorded in the study is provided in Table 4 below. Detailed information regarding activities to be performed at each visit is provided in Section 7.2, below.

Table 4. Schedule of Events Overview

Period	Screen	Treatment																Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**				
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**					
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q4 Weeks**	**Q12 Weeks**	**End of Treatment**	**Immediate post-treatment**	**Long-term**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**			
Informed consent	X																			
Medical history	X																			
Histopathology review	X																			
Serum virology	X																			
Coagulation	X																			
Urinalysis	X																			
β-HCG	X																			
PPD																				
HRQL – FACT-Lym		X		X		X		X	X	X	X	X	X	X	X		X			
Study drug return/ accounting				X		X		X	X	X	X		X		X		X	X		
Adverse events[d,e]		X		X		X		X	X	X	X	X	X	X	X		X	X	X	X
Concomitant medications	X	X		X		X		X	X	X	X	X	X	X	X		X	X		
Performance status	X	X		X		X		X	X	X	X	X	X	X	X		X	X		

Period	Screen	Treatment																Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**				
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**					
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q4 Weeks**	**Q12 Weeks**	**End of Treatment**	**Immediate post-treatment**	**Long-term**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**			
Vital signs	X	X		X		X		X	X	X	X	X	X	X	X		X	X		
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
Pharmacodynamics		X		X		X		X	X	X	X	X	X	X	X		X	X		
Drug dispensing		X		X		X		X	X	X	X		X		X		X			
Physical examination	X								X									X		
12-lead ECG	X								X									X		
Immunophenotyping		X				X			X		X		X		X		X	X		
Serum immunoglobulins		X				X			X		X		X		X		X	X		
Radiology assessments (CT/MRI)	X					X			X		X		X		X		X	X		
Bone marrow biopsy/ aspirate[a]	X					X[a]			X[a]		X[a]		X[a]		X[a]		X[a]			
SPEP (IgM monoclonal protein)[b]	X					X			X		X		X		X		X	X		

Period	Screen	Treatment																Follow-up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16+**				
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**30**	**36**	**42**	**48**					
Study Day	**Within -28 Days**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**113**	**141**	**169**	**211**	**253**	**295**	**337**	**Q4 Weeks**	**Q12 Weeks**	**End of Treatment**	**Immediate post-treatment**	**Long-term**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**			
Idelalisib dosing in clinic		X		X		X			X											
Limited pharmaco-kinetics		X		X		X			X											
PPD																				
Monthly CMV testing																X		X		
Immune-monitoring labs																	X	X		

Study Procedures and Timing[c]

a Required at screening. If disease present at baseline, to be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate does not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.

b For subjects with WM only, performed locally per standard of care.

c For detailed information regarding activities to be performed at each visit, see Section 7.2.

d Assessment of Diarrhea/Colitis: obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents.

e Assessment of Diarrhea/Colitis: perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).

Abbreviations: β-HCG, beta human chorionic gonadotropin; HRQL, health-related quality of life; FACT-Lym, Functional Assessment of Cancer Therapy-Lymphoma; ECG, electrocardiogram; CT, computed tomography; LPL, lymphoplasmacytoid lymphoma; WM, Waldenstroms Macroglobulinemia, MRI, magnetic resonance imaging; SPEP, serum protein electrophoresis; CR, complete response

7.2. Explanation of Study Visits

The specific assessments to be performed at each visit are detailed below.

For visits at which HRQL results are obtained, it is important that the subject be administered the FACT-Lym before any other procedures are performed and before any study-related information is communicated to the subject; this is necessary to avoid biasing the HRQL responses provided by the subject. Once the subjects had completed the HRQL assessments, the remaining procedures may be performed.

At visits involving idelalisib administration and pharmacokinetic sampling in the clinic, care should be taken to perform procedures with the appropriate timing relative to idelalisib administration. The actual sample collection times of pharmacokinetic blood specimens should be recorded. If a heparinized venous catheter is placed for sample collection in order to avoid repeated needle sticks, at least 2 mL of blood should be removed and discarded prior to each sample collection in order to avoid heparin contamination of the sample.

At visits designated as laboratory only visits (Visits 3, 5, and 7), subjects will have laboratory assessments that may be performed at the investigational site or at an accredited local laboratory or clinic that is convenient for the subject/caregiver. If blood is collected at a local laboratory, samples are not to be analyzed at the local laboratory. For these visits, subjects and/or caregivers will be provided with central laboratory kits that will contain materials necessary for the collection and shipment of the laboratory samples by the local laboratory clinic to the central laboratory.

CT or MRI imaging of the neck, chest, abdomen, and pelvis will be performed as a component of tumor assessments throughout the study; the same method of assessment (CT or MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and while on study.

7.2.1. Visit 1 and Screening Period (Clinic Visit)

The initial screening visit is designated as Visit 1. At Visit 1, the investigator must inform each prospective study participant of the nature of the study, explain the potential risks, and obtain written informed consent from the study candidate and/or legal guardian prior to performing any study-related screening procedures. Once the informed consent document has been signed, the subject may undergo the screening procedures.

In order to optimize scheduling convenience for the subject and for the investigational staff, screening procedures may be performed over as many days as necessary provided that screening is completed within 4 weeks prior to initiation of treatment.

The tests and evaluations outline in Table 5 will be performed at Visit 1 or during the screening period prior to study enrollment and initiation of study treatment.

Table 5. Procedures and Assessments at Visit 1 (During Screening Period)

Assessment or Procedure	Explanation
Informed consent	To be obtained before any screening procedures are initiated (unless procedures are performed as standard of care prior to informed consent)
Medical history	Including relevant information regarding iNHL histology, iNHL history, current iNHL Ann Arbor staging, current FLIPI score, reasons for treatment, prior therapies for iNHL, documentation that iNHL is refractory to rituximab and alkylating agents, and past history of hepatobiliary disease
Concomitant medications	Recording of ongoing concomitant medication use
Histopathology review	Transmission of histopathology materials for confirmation of iNHL. Results not required for enrollment.
Performance status	Using Karnofsky performance status criteria and ECOG for study inclusion criteria (see Appendix D)
Physical examination	Including height, weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
12-lead ECG	To be obtained while subject is resting in the supine position
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Serum virology	Including HBV antigen, HCV antibody, HIV antibody, CMV serology; if HBV antigen or HCV antibody are positive, subjects must be evaluated for the presence of circulating HBV or HCV viral RNA
Coagulation	aPTT, PT
Urinalysis	Dipstick for pH, protein, glucose, blood, nitrite, leukocytes
β-HCG	Women of childbearing potential only
SPEP	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis to be performed within 28 days prior to initiation of study treatment at Visit 2; the same method of assessment (CT or MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and while on study
Bone marrow biopsy and aspirate	Required to assess presence or absence of bone marrow involvement with lymphoma; may be omitted if already performed within 6 weeks prior to initiation of study treatment

Abbreviations: NHL, indolent non-Hodgkin lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; CMV, cytomegalovirus; RNA, ribonucleic acid; aPTT, activated partial thromboplastin time; PT, partial thromboplastin time; β-HCG, beta human chorionic gonadotropin; SPEP, serum protein electrophoresis; Ig, immunoglobulin; LPL, lymphoplasmacytoid lymphoma; WM, Waldenstroms Macroglobulinemia, CT, computed tomography; MRI, magnetic resonance imaging

7.2.2. Visit 2 (Day 1) (Clinic Visit)

Subjects will be medically assessed to determine if they still meet eligibility criteria and can initiate study treatment. The procedures outlined in Table 6 will be performed at Visit 2 (Day 1).

Table 6. Procedures and Assessments at Visit 2 (Day 1)

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since the initiation of the screening period
Concomitant medications	Recording of concomitant medication use since the initiation of the screening period
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils,basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Circulating cells for immuno-phenotyping	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins	Including quantitative levels of IgA, IgE, IgG, and IgM
PPD	
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the last meal [if any] and of the date and actual clock time of blood collection)
Idelalisib Administration	
Idelalisib administration	First dose of idelalisib study drug to be administered to the subject (with recording of the date and actual clock time of the idelalisib administration)
Post-Dose Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours (± 5 minutes) after idelalisib administration (with recording of the date and actual clock time of blood collection)
PPD	
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of Visit 4.

Abbreviations: FACT-Lym, Functional Assessment of Cancer Therapy; Lymphoma HRQL, health-related quality of life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; Ig, immunoglobulin; DNA, deoxyribonucleic acid; RNA, ribonucleic acid

7.2.3. Visit 3 (Day 15) (Laboratory Visit)

The procedures outlined in Table 7 will be performed at Visit 3 (Day 15 [±2 days]).

Table 7. Procedures and Assessments at Visit 3 (Day 15)

Assessment or Procedure	Explanation
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including ALT, AST, ALP, GGT, total bilirubin, LDH

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase

7.2.4. Visit 4 (Day 29) (Clinic Visit)

The procedures outlined in Table 8 will be performed at Visit 4 (Day 29 [±2 days]).

Table 8. Procedures and Assessments at Visit 4 (Day 29)

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 2
Concomitant medications	Recording of concomitant medication used since Visit 2
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of idelalisib (should be the prior evening dose) and whether that dose of idelalisib was taken within 1 hour after a meal
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the last meal [if any] and of the date and actual clock time of blood collection)
Idelalisib Administration	
Idelalisib administration	Dose of idelalisib study drug to be administered to the subject (with recording of the date and actual clock time of idelalisib administration)
Post-Dose Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours (± 5 minutes) after idelalisib administration (with recording of the date and actual clock time of blood collection)
PPD	
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of Visit 6.
Scheduling of Visit 6 radiology assessment	CT or MRI imaging of chest, abdomen, and pelvis to be scheduled for Visit 6; the same method of assessment (CT or MRI) should be used as was used at baseline

Abbreviations: FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging

7.2.5. Visit 5 (Day 43) (Laboratory Visit)

The procedures outlined in Table 9 will be performed at Visit 5 (Day 43 [±2 days]).

Table 9. Procedures and Assessments at Visit 5 (Day 43)

Assessment or Procedure	Explanation
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including ALT, AST, ALP, GGT, total bilirubin, LDH

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase

7.2.6. Visit 6 (Day 57) (Clinic and Radiology Visit)

The procedures outlined in Table 10 will be performed at Visit 6 (Day 57 [±2 days]).

Table 10. Procedures and Assessments at Visit 6 (Day 57)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis on day of visit or within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline and the assessment should be done even if study drug has been interrupted.
Pre-Dose Procedures and Assessments	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 4
Concomitant medications	Recording of concomitant medication used since Visit 4
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of idelalisib (should be the prior evening dose) and whether that dose of idelalisib was taken within 1 hour after a meal
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Circulating cells for immuno-phenotyping	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins	Including quantitative levels of IgA, IgE, IgG, and IgM
SPEP	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate did not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the last meal [if any] and of the date and actual clock time of blood collection)
Idelalisib Administration	
Idelalisib administration	Dose of idelalisib study drug to be administered to the subject (with recording of the date and actual clock time of idelalisib administration)
Post-Dose Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours (±5 minutes) after idelalisib administration (with recording of the date and actual clock time of blood collection)
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; Ig, immunoglobulin; SPES, serum protein electrophoresis; LPL, lymphomplasmacytoid lymphoma; WM- Waldenstroms Macroglobulinemia, CR, complete response

7.2.7. Visit 7 (Day 71) (Laboratory Visit)

The procedures outlined in Table 11 will be performed at Visit 7 (Day 71 [±2 days]).

Table 11. Procedures and Assessments at Visit 7 (Day 71)

Assessment or Procedure	Explanation
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including ALT, AST, ALP, GGT, total bilirubin, LDH

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase

7.2.8. Visit 8 (Day 85) (Clinic Visit)

The procedures outlined in Table 12 will be performed at Visit 8 (Day 85 [±2 days]).

Table 12. Procedures and Assessments at Visit 8 (Day 85)

Assessment or Procedure	Explanation
Pre-Dose Procedures and Assessments	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 6
Concomitant medications	Recording of concomitant medication used since Visit 6
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of idelalisib (should be the prior evening dose) and whether that dose of idelalisib was taken within 1 hour after a meal
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home
Instruction regarding dosing at next full clinic visit	Instruction to the subject that the morning dose of idelalisib should not be taken on the day of Visit 9.
Scheduling of Visit 9 radiology assessment	CT or MRI imaging of chest, abdomen, and pelvis to be scheduled for the Visit 9 radiology assessment; the same method of assessment (CT or MRI) should be used as was used at baseline

Abbreviations: FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging

7.2.9. Visit 9 (Day 113) (Clinic and Radiology Visit)

The procedures outlined in Table 13 will be performed at Visit 9 (Day 113 [±3 days]).

Table 13. Procedures and Assessments at Visit 9 (Day 113)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis on day of visit or within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline
Pre-Dose Procedures and Assessments	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since Visit 8
Concomitant medications	Recording of concomitant medication used since Visit 8
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of idelalisib (should be the prior evening dose) and whether that dose of idelalisib was taken within 1 hour after a meal
Physical examination	Including height, weight, evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
12-lead ECG	To be obtained while subject is resting in the supine position
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Circulating cells for immuno-phenotyping	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins	Including quantitative levels of IgA, IgE, IgG, and IgM
SPEP	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate did not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Idelalisib pharmacokinetics	Pre-dose collection of plasma sample for idelalisib pharmacokinetics (with recording of the date and actual clock time of the last meal [if any] and of the date and actual clock time of blood collection)
Idelalisib Administration	
Idelalisib administration	Dose of idelalisib study drug to be administered to the subject (with recording of the date and actual clock time of idelalisib administration)
Post-Dose Procedures and Assessments	
Idelalisib pharmacokinetics	Post-dose collection of plasma sample for idelalisib pharmacokinetics at 1.5 hours (±5 minutes) after idelalisib administration (with recording of the date and actual clock time of blood collection)
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; Ig, immunoglobulin; SPEP, serum protein electrophoresis; LPL, lymphoplasmacytoid lymphoma, WM, Waldenstroms Macroglobulinemia; CR, complete response;

7.2.10. Visit 10 (Day 141) (Clinic Visit)

The procedures outlined in Table 14 will be performed at Visit 10 (Day 141 [±3 days])

Table 14. Procedures and Assessments at Visit 10 (Day 141)

Assessment or Procedure	Explanation
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug. Recording of the date and actual clock time of the last prior subject self-administration of idelalisib (should be the prior evening dose) and whether that dose of idelalisib was taken within 1 hour after a meal
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Drug dispensing	Dispensing of 4-week supply of idelalisib study drug to the subject with instructions for self-administration at home
Scheduling of Visit 11 radiology assessment	CT or MRI imaging of chest, abdomen, and pelvis to be scheduled for Visit 11; the same method of assessment (CT or MRI) should be used as was used at baseline

Abbreviations: FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life ALT; alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging

7.2.11. Visit 11 (Day 169) (Clinic and Radiology Visit)

The procedures outlined in Table 15 will be performed at Visit 11 (Day 169 [±3 days]).

Table 15. Procedures and Assessments at Visit 11 (Day 169)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis on day of visit or within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline
During-Visit Assessments and Procedures	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting returned study drug
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Circulating cells for immuno-phenotyping	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins	Including quantitative levels of IgA, IgE, IgG, and IgM
SPEP	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate did not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Drug dispensing	Dispensing of 12-week supply of idelalisib study drug to the subject with instructions for self-administration at home

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FACT-Lym , Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life ; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CR = complete response; Ig, immunoglobulin; SPEP, serum protein electrophoresis; LPL, lymphoplasmacytoid lymphoma, WM, Waldenstroms Macroglobulinemia; CR, complete response

7.2.12. Visits 12 and 14 (Days 211 and 295) (Clinic Visits)

The procedures outlined in Table 16 will be performed at Visits 12 and 14 (Days 211] and 295 [±3 days])

Table 16. Procedures and Assessments at Visits 12 and 14 (Days 211 and 295)

Assessment or Procedure	Explanation
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Scheduling of next-visit radiology assessment	CT or MRI imaging of chest, abdomen, and pelvis to be scheduled to occur within 1 week prior to the next clinic visits (Visits 13 and 15); the same method of assessment (CT or MRI) should be used as was used at baseline

Abbreviations: FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life ; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CT, computed tomography; MRI, magnetic resonance imaging

7.2.13. Visits 13, 15, etc. (Days 253, 337, and Every 12 Weeks) (Clinic and Radiology Visit)

The procedures outlined in Table 17 will be performed at Visit 13 (Day 253 [±3 days]) and at Visit 15, etc. (Days 337 and every 12 weeks thereafter [±7 Days]).

Table 17. Procedures and Assessments at Visits 13, 15, etc. (Days 253, 337, and Every 12 Weeks)

Assessment or Procedure	Explanation
Pre-Visit Tumor Assessment	
Radiology assessment	CT or MRI imaging of neck, chest, abdomen, and pelvis on day of visit or within 1 week prior to the visit; the same method of assessment (CT or MRI) should be used as was used at baseline
During-Visit Assessments and Procedures	
FACT-Lym	HRQL instrument (Appendix C) to be administered before any other procedures are performed and before any study-related information is communicated to the subject
Adverse events[a, b]	Recording of adverse events occurring since prior visit
Concomitant medications	Recording of concomitant medication used since prior visit
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Compliance	Counting of returned study drug
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
Hematology	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
Pharmacodynamic markers	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Circulating cells for immuno-phenotyping	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins	Including quantitative levels of IgA, IgE, IgG, and IgM
SPEP	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Bone marrow biopsy and aspirate	To be performed post-baseline to confirm response category in subjects with potential CR by radiological assessments. If the baseline bone marrow biopsy/aspirate did not show lymphoma involvement, it is not necessary to obtain a follow-up bone marrow biopsy/aspirate to establish CR.
Drug dispensing	Dispensing of12-week supply of idelalisib study drug to the subject with instructions for self-administration at home
Scheduling of next-visit radiology assessment	CT or MRI imaging of chest, abdomen, and pelvis to be scheduled to occur within 1 week prior to the next clinic visit (Visit 15 and every 12 weeks therafter); the same method of assessment (CT or MRI) should be used as was used at baseline
Monthly CMV Testing	CMV surveillance must be conducted approximately every 4 weeks.
Immune-monitoring Labs	• Lymphocyte subset panel using flow cytometry (immunophenotyping) • Quantitative immunoglobulins: IgG, IgM, IgA • Serum CH50 level

a Assessment of Diarrhea/Colitis: obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents.

b Assessment of Diarrhea/Colitis: perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FACT-Lym, Functional Assessment of Cancer Therapy: Lymphoma; HRQL, health-related quality of life; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; Ig, immunoglobulin; SPEP, serum protein electrophoresis; LPL, lymphoplasmacytoid lymphoma, WM, Waldenstroms Macroglobulinemia; CR, complete response

7.2.14. End-of-Treatment Visit (Clinic Visit)

At the time of discontinuation from the treatment, the subject should have the following procedures and assessments performed. The radiology assessment should be obtained if the last radiology assessment was >4 weeks from the end-of-treatment visit. ECG and laboratory evaluations should be obtained if these had not been obtained within the preceding 2 weeks.

Table 18. Procedures and Assessments at End-of-Treatment Visit

Assessment or Procedure	Explanation
Radiology assessment[a]	CT or MRI imaging of neck, chest, abdomen, and pelvis; the same method of assessment (CT or MRI) should be used as was used at baseline
Adverse events [c,d]	Recording of adverse events occurring since prior visit; if a clinically significant adverse event or abnormal result is observed that is not resolved by the end-of treatment visit, repeat evaluations should be performed to document resolution or stabilization of the abnormality
Concomitant medications	Recording of concomitant medication used since prior visit
Performance status	Using Karnofsky performance status criteria (see Appendix D)
Physical examination	Including evidence of palpable lymphadenopathy, hepatomegaly, and/or splenomegaly
Compliance	Counting of used and unused study drug since last compliance assessment and return of all study drug
Vital signs	Including weight, temperature, resting systolic and diastolic blood pressure while sitting, resting heart rate while sitting
12-lead ECG[b]	To be obtained while subject is resting in the supine position
Hematology[b]	Including hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count
Serum chemistry[b]	Including sodium, potassium, chloride, glucose, urea, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, ALP, GGT, total bilirubin, LDH, uric acid, cholesterol, triglycerides
SPEP[b]	Including serum IgM monoclonal protein level (subjects with WM only; performed locally per standard of care)
Pharmacodynamic markers[b]	Collection of plasma and serum for evaluation of circulating chemokines and cytokines
Circulating cells for immuno-phenotyping[b]	Including quantitation of absolute number of CD4+, CD8+, CD16/CD56+ and CD19+ cells by flow cytometry
Serum immunoglobulins[b]	Including quantitative levels of IgA, IgE, IgG, and IgM
Monthly CMV Testing[e]	CMV surveillance must be conducted approximately every 4 weeks.
Immune-monitoring labs	• Lymphocyte subset panel using flow cytometry (immunophenotyping) • Quantitative immunoglobulins: IgG, IgM, IgA • Serum CH50 level

a The radiology assessment should be obtained if the last radiology assessment was >4 weeks from the end-of-treatment visit.
b ECG and laboratory evaluations should be obtained if these had not been obtained within the preceding 2 weeks.
c Assessment of Diarrhea/Colitis: obtain history of onset and duration of diarrhea, including description of number of stools and stool composition (eg, watery, bloody, nocturnal), travel history, dietary changes and a medication review to identify possible diarrheogenic agents.
d Assessment of Diarrhea/Colitis: perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness (ie, evaluate for sepsis, bowel obstruction, dehydration).
e Unless already performed within 4 weeks of the End of Treatment visit.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; ECG, electrocardiogram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; SPEP, serum protein electrophoreis; LPL, lymphoplasmacytoid lymphoma, WM, Waldenstroms Macroglobulinemia; Ig, immunoglobulin

7.2.15. Immediate Post-Treatment Safety Follow-up

After the last dose of study treatment subjects should be followed for any drug-related adverse events and/or ongoing serious adverse events until those events have resolved or become stable, whichever occurs later. Follow-up may be obtained in person or by telephone contact.

7.2.16. Long-Term Follow-up

Long-term post-treatment follow-up will be obtained for all subjects, including those who prematurely withdraw from study treatment.

The long-term post-treatment follow-up will be conducted (as measured from the last dose of study drug) at ~6-month intervals during Year 1 and Year 2, and at ~12-month intervals during Years 3, 4, and 5. Data on subject survival, date of disease progression if processgion occurred after the end-of-treatment, post-idelalisib therapies for iNHL, and occurrence of new non-iNHL-related health problems (eg, chronic hepatic abnormalities, endocrine disorders, renal dysfunction, etc) will be collected from all subjects who receive ≥1 dose of study drug. The information will be gathered during a routine clinic visit or other contact with the subject, or via telephone. These data will be collected in the source documents (eg, subject medical record) and transcribed into the electronic case report form. Any unsuccessful efforts to contact the subject (eg, dates of unanswered phone calls, return of certified letter sent to subject's home, etc) will be documented.

7.3. Sample Storage

7.4. Blood Collection

Computations of blood drawing requirements for this study are shown in Table 19. The maximum amount of blood to be drawn at a visit is ≤82 mL and the total amount of blood to be drawn over the initial 52-week study period (including the 4-week screening period and through Week 48 of the study) is ~379 mL. For a 40-kg person (the smallest participant expected to enroll in the study), this equates to maximum blood volume per body weight per visit of ~2.1 mL/kg and a total blood volume per body weight per average 6-week period of ~1.1 mL/kg. These quantities of blood are within accepted limits of 3.0 mL/kg of body weight for a single blood draw and 7.0 mL/kg of body weight for any 6-week period [National Institutes of Health 2003].

Specific details regarding blood sample collection and processing requirements will be provided separately in the central laboratory manual.

Table 19. Blood Drawing Requirements Through Visit 15 (Week 48)

Test	Sample Type	Tube Type	Blood Per Tube (mL)	Tubes (n)		Blood Volume (mL)	
				Maximum Per Visit	Total in Study[a]	Maximum Per Visit	Total in Study[a]
Hematology	Plasma	K_2-EDTA	3	1	15	3	45
Serum chemistry (including β-HCG)	Serum	Clot	5	1	15	5	75
Coagulation	Plasma	Citrate	4	1	1	4	4
Serum virology	Serum	Clot	9	1	1	9	9
PPD							
Pharmacodynamic markers	Plasma	K_2-EDTA	5	1	11	5	55
	Serum	Clot	5	1	11	5	55
Circulating cells for immuno-phenotyping	Plasma	K_2-EDTA	4	1	6	4	24
Serum immunoglobulins	Serum	Clot	5	1	6	5	30
Idelalisib pharmacokinetics (limited, all subjects)	Plasma	K_2-EDTA	2	2	8	4	16
PPD							
Total						82	369

a Computed for initial 52-week period (considering 4 weeks for screening and 48 weeks on study)
Abbreviations: β-HCG, beta human chorionic gonadotropin; K_2-EDTA, potassium-ethylenediaminetetraacetic acid; DNA, deoxyribonucleic acid; RNA, ribonucleic acid

Serum and plasma may be retained for subjects who have provided specific informed consent for sample banking.

7.5. Study Parameter Selection Rationale

The planned study assessments and timing have been selected as appropriate for screening of subjects, for determination of idelalisib-related or disease-related toxicities, for dose modification during the study, for characterization of drug exposure and desired pharmacological effects, and for evaluation of drug activity. The scheduling of testing is designed to collect a complete safety and pharmacology data set while maintaining subject tolerance of study procedures. The planned schedule of tumor assessments is consistent with expected rate of changes and appropriately balances precise measurement of tumor control with the expense and subject inconvenience associated with radiological procedures. For discussion of the rationale for endpoint selection, see Section 3.5.

8. ACTIVITY AND SAFETY ASSESSMENTS

8.1. Tumor Size Assessments

The determination of iNHL response and progression will be based on standardized criteria {Cheson 2007, Owen 2013}. Treatment decisions by the investigator will be based on these assessments.

8.1.1. Timing of Assessments

During screening, imaging-based tumor assessments should be performed within 28 days prior to the start of treatment. On-study tumor assessments should be performed at ~8- to 12-week intervals as dictated by the study protocol. An end-of-treatment tumor assessment (if the subject withdraws from the study for reasons other than tumor progression on a routine imaging/scan) should be performed if the last assessment was performed >4 weeks prior to end-of-treatment visit.

8.1.2. Method of Assessment

Imaging-based evaluation is preferred to evaluation by clinical examination. CT or MRI scans are the required methods for tumor assessments. PET scanning will not be a required component of response assessment in this study. Clinical palpation, chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scan, or tumor markers will not be considered for response assessment.

The same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. CT or MRI of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤10 mm in slice thickness contiguously.

All relevant clinical and radiographic information required to make each tumor status assessment must be made available for source verification and for submission to the IRC (see Section 11.2).

For subjects with WM, serum Monoclonal IgM as assessed by SPEP will only be considered if baseline total serum IgM quantitation by nephelometry is not available. The same laboratory method for IgM assessment within a given subject should be used throughout the study.

8.1.3. Identification of Index and Non-Index Tumor Lesions at Baseline

At baseline, tumor lesions will be categorized as index lesions or non-index lesions as described below.

Up to 6 lesions (eg, lymph nodes, liver or spleen nodules, and/or other circumscribed extra-nodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals during treatment. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter [LD] × the longest perpendicular diameter [LPD]) will be recorded (in cm) for each index lesion. The product of the perpendicular diameters (PPD) will be calculated. The PPDs and the sum of the products (SPDs) for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which objective tumor response will be characterized during treatment. The nadir SPD and nadir LDs of individual lesions will be used as references by which objective tumor progression will be characterized during treatment. All PPD and SPD measurements will be reported in centimeters squared.

8.1.3.1. Index Lesions

8.1.3.1.1. Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is > 1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥1.0 cm and the LPD also being ≥ 1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- Large nodal lesions have an LD that is >1.5 cm and an LPD that is ≥1.0 cm.
- Small nodal lesions have an LD that is >1.0 cm and ≤1.5 cm and an LPD that is >1.0 cm.

Index lesions measuring >1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

8.1.3.1.2. Extra-Nodal Index Lesions

An extra-nodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extra-nodal mass of any size is considered abnormal. It is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥ 1.0 cm and the LPD also being ≥1.0 cm.

8.1.3.2. Non-Index Lesions

Any other measurable and abnormal nodal or extra-nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of iNHL such as nodal lesions or extra-nodal lesions with both diameters < 1.0 cm, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, or lesions with artifacts may be considered as non-index disease.

The presence or absence of non-index disease should be recorded at baseline and at the stipulated intervals during treatment. If present at baseline, up to 6 non-index lesions should be recorded. The non-index disease at baseline will be used as a general reference to further characterize

regression or progression of lymphoma during assessments of the objective tumor response during treatment. Measurements are not required and these lesions should be followed as "present" or "absent".

8.1.4. Follow-up of Index and Non-Index Tumor Lesions

8.1.4.1. Nodal Lesions

At follow-up time points, the LDs for individual lesions and the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters >0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2.

New or enlarging nodal lesions that are still ≤1.0 cm by ≤1.0 cm will not be considered to represent recurrent or progressive disease. A new node that measures >1.5 cm in any diameter or a new node that measures >1.0 cm to ≤1.5 cm in the LD and measures >1.0 cm in the LPD will be considered progressive disease.

In cases in which a large lymph node mass has split into multiple components, all subcomponents regardless of size will be used in calculating the SPD. Progression of the lesion will be based on the SPD of all sub-components. Lesion sub-components will have PPDs calculated. Similarly, lesion sub-components that are visible but neither abnormal nor measurable will have the default PPD of 1.0 cm^2 (1.0 cm × 1.0 cm) used in calculating the SPD.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

8.1.4.2. Extra-nodal Lesions

At follow-up time points, the LDs of each single extra-nodal lesion and the SPD of all extra-nodal index lesions will be considered. Because extra-nodal index lesions that have one or both diameters <1.0 cm and >0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extra-nodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extra-nodal lesion that had resolved (ie, had a PPD of 0 cm^2) subsequently reappears, the subject will be considered to have progressive disease. A new extra-nodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernable to the radiologist by CT scan will be considered progressive disease.

8.1.5. Definitions of Tumor Response and Progression

Responses will be categorized as CR, PR, minor response (MR) for subjects with WM only, stable disease (SD), or progressive disease (PD). In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status. A response category of no disease (ND) is included for situations in which there is no evidence of tumor either at baseline or on treatment.

The best overall response will be determined. The best overall response is the best response recorded from the start of treatment until progressive disease/recurrence (taking as reference for PD the smallest measurements recorded since treatment started). Subjects with NE or ND will be counted as failures in the analyses of tumor response. Where imaging data are available, these data will supersede physical examination data in determining tumor status.

8.1.5.1. Response Categories

8.1.5.1.1. Complete Response

To satisfy criteria for complete response (CR), all of the following criteria must be met:

- No evidence of new disease
- Regression of all index nodal and extra-nodal masses to normal size (≤1.5 cm in the LD for nodes that were considered large at baseline and ≤1.0 cm in the LD for nodes that were considered small at baseline) (see Section 8.1.3.1.1 for definitions of large and small nodes)
- Regression to normal of all nodal non-index disease and disappearance of all detectable non-nodal, non-index disease
- Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new organ enlargements
- Morphologically negative bone marrow based on an adequate unilateral core biopsy (>20 mm unilateral core); if the sample is indeterminate by morphology, it should be negative by immunohistochemistry
- If PET performed (not required), no evidence of residual disease
- If the subject has WM, disappearance of monoclonal protein by immunofixation

8.1.5.1.2. Partial Response

To satisfy criteria for partial response (PR), all of the following criteria must be met except for subjects with WM as noted below:

- No evidence of new disease

- A ≥50% decrease from baseline in the SPD of the index nodal and extra-nodal lesions (eg, splenic or hepatic nodules)
- No increase in the size of non-index nodes or non-measurable disease
- No increase in the size of the liver or spleen and no new organ enlargements.
- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extra-nodal masses
- If PET performed (not required):
  - Typically FDG-avid lymphoma: if no pretreatment PET scan or if the PET scan was positive before therapy, the on-treatment PET is positive in ≥1 previously involved site.
  - Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during treatment. If the PET scan was positive before therapy, the on-treatment PET is positive in ≥1 previously involved site.
- For subjects with WM
  - ≥50% decrease from baseline in monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry
  - Any decrease from baseline in the SPD of the index nodal and extral-nodal lesions (eg, splenic or hepatic nodules)

8.1.5.1.3. Minor Response (WM only)

To satisfy criteria for MR, the following criteria must be met:

- A ≥25% but <50% decrease from baseline in either monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry
- No increase from baseline in the SPD of the index nodal and extra-nodal lesions (eg, splenic or hepatic nodules)
- No increase in the size of non-index nodes or non-measurable disease
- No increase in the size of the liver or spleen and no new organ enlargements

8.1.5.1.4. Stable Disease

To satisfy criteria for stable disease (SD), all of the following criteria must be met:

- No evidence of new disease

- Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD
- If the subject has WM, neither a sufficient decrease from baseline in either monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry to qualify for MR or PR nor a sufficient increase from nadir in either monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry to qualify for PD

8.1.5.1.5. Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- Evidence of any new disease that was not present at baseline:
  - A new node that measures >1.5 cm in any diameter
  - A new node that measures >1.0 cm to ≤1.5 cm in the LD and >1.0 cm in the LPD
  - Reappearance of an extra-nodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)
  - A new extranodal lesion of any size
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma).
    Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.
- Evidence of worsening of nodal or extra-nodal index lesions:
  - Increase from the nadir by ≥50% in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
- Unequivocal increase in the size of non-index lesions or non-measurable disease (eg, pleural effusions or bone lesions)
- An unequivocal increase in the size of the liver, spleen or other organ
- If PET performed (not required):
  - The appearance of any new lesion compatible with lymphoma with confirmation by other radiographic or histological modalities.
  - The reappearance of any activity in a pre-existent lesion that meets size criteria for a new lesion on CT

- If the subject has WM, a ≥25% increase from the nadir in either monoclonal IgM concentration by SPEP or total serum IgM quantitation by nephelometry (with confirmation by a repeat measurement). An absolute increase of at least 0.5 gram/dL is required to define progression.

Note: If there is uncertainty regarding whether there is true progression, the subject may continue study treatment and remain under close observation (eg, evaluated at 4-week intervals). If subsequent evaluations suggest that the subject is experiencing progression, then the date of progression should be the timepoint at which progression was first identified.

8.1.5.1.6. Non-Evaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images.
- For subjects with WM, on-study monoclonal IgM concentration by serum protein electrophoresis (SPEP) or total serum IgM quantitation by nephelometry is missing in a subject with baseline IgM available. If the baseline IgM value is missing, IgM will not be considered for the on-study disease assessments.

Note: A time-point will be considered to have a response of NE if any index lesion is missing. PD may be assigned at any time point regardless of the extent of missing index or non-index lesions. Missing non-index lesions will not impact the ability to assess for response or disease progression.

8.1.5.1.7. No Disease

In a subject who does not have evidence of PD, the occurrence of all of the following conditions indicates a response status of ND:

- Index disease absent at both baseline and on-treatment
- Non-index disease absent at both baseline and on-treatment
- Enlargement of the liver and spleen absent at both baseline and on-treatment

8.2. Adverse Event Assessments

8.2.1. Adverse Event Definitions

8.2.1.1. Adverse Events

By convention, an adverse event is any untoward medical occurrence in a trial subject who is administered a drug or biologic (medicinal product) or who is using a medical device; the event does not necessarily have a causal relationship with study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For this protocol, untoward medical occurrences that should be reported as adverse events include the following:

- All adverse events that are suspected to be due to study drug
- All reactions from medication abuse, withdrawal, sensitivity, or toxicity
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory or ECG abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a subject with jaundice) should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as adverse events.
- A preexisting condition (eg, allergic rhinitis) must be noted on the appropriate baseline CRF but should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the source documents. If a surgical procedure was planned prior to entry into the trial, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an adverse event. Note that, as described in Section 8.2.1.2, any in-patient hospitalization occurring as the consequence of an adverse event during the study period should be reported as a serious adverse event.
- Each adverse event is to be classified as serious or nonserious.

8.2.1.2. Serious Adverse Events

A serious adverse event is an untoward medical occurrence, regardless of whether or not it is considered related to the study medication, which results in:

- Death (ie, all deaths on treatment or within 30 days after last study drug administration), excluding deaths due to disease progression. Deaths occurring later than 30 days following the last dose need not be reported as serious adverse events unless they are a result of an event that started within the time frame covered by the on-study definition. The reported

adverse event should be the event that caused the death. Death is the outcome of this serious adverse event. In addition, any adverse event resulting in death that occurs subsequent to the adverse event-reporting period and that the investigator assesses as possibly related to the study drug should also be reported as serious.

- Life-threatening situation (ie, with an immediate risk of death from the event as it occurred). It does not include an event that, had it occurred in a more serious form, might have caused death.

- In-patient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital are not considered as serious.

- Persistent or significant disability/incapacity

- Congenital anomaly/birth defect

- Any other adverse event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent any of the outcomes listed above should be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment administration in an emergency room or at home, new cancers or blood dyscrasias, or convulsions that do not result in insubject hospitalization, or the development of drug dependency or drug abuse.

- An event needs not be reported as a serious adverse event if it exclusively represents a relapse or an expected change or progression of the baseline malignant disease.

8.2.1.3. Unexpected Adverse Events

Unexpected adverse events are defined as those events that were not previously reported with study drug as referenced in the protocol, investigator brochure, consent form, or package insert, or that are symptomatically and pathophysiologically related to a known toxicity but differ because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed (eg, included in the investigator brochure, study protocol, informed consent document, or package insert) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

The investigator brochure provides a summary of the safety profile of idelalisib based on a review of the available safety data from studies in healthy volunteers and in subjects with cancer. Consistent with the definitions outlined in this section, the study sponsor will consider the information provided in the investigator brochure when determining whether a drug-related serious adverse event is unexpected. In making this determination, the study sponsor will consider the uniqueness, type, severity, and specificity of the event relative to past events of similar nature, recognizing that an event that might be considered expected in a subject with one condition might be considered unexpected in a subject with another condition. This assessment will be used in determining the need for expedited regulatory reporting.

8.2.2. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events at each scheduled clinic visit or during each telephone contact with the subject following initiation of study treatment. The type of question asked should be open-ended, eg, *"Have you had any new health problems?"* or a similar type of query.

8.2.3. Adverse Event Recording

All adverse events (both serious and nonserious) that occur in subjects during the adverse event reporting period must be recorded, whether or not the event is considered drug related. If the subject is a screen failure, then only adverse events related to study procedures should be recorded. In addition, any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an adverse event.

All adverse events are to be recorded in the source documents and on the CRF using concise medical terminology; whenever possible terms contained in MedDRA should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or nonserious (see Section 8.2.1.2)
- Relationship to study drug (see Section 8.2.4)
- Severity of the event (see Section 8.2.5)
- Onset date and time
- Resolution date and time, or date and time of death
- Action taken
- Outcome of the event

Classification of the event as serious or nonserious determines the reporting procedures to be followed.

8.2.4. Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in Table 20 below, an evaluation of whether an adverse event can be attributed to the study drug should be provided.

Table 20. Relationship of Study Drug to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study drug seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study drug, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study drug administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

8.2.5. Grading of Severity of Adverse Event

The severity of adverse events will be graded using the CTCAE, Version 3.0 (refer to *http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf*). For each episode, the highest severity grade attained should be reported

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 21.

Table 21. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

Note the distinction between the seriousness and the severity of an adverse event. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.2.1.2 above.

8.2.6. Follow-up of Unresolved Adverse Events

All adverse events should be followed until resolution, the investigator assesses them as chronic or stable, or the end-of-treatment visit. All related adverse events should be followed until resolution or 30 days following the last dose of study drug. The investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. A subject withdrawn from the study because of an adverse event must be followed by the investigator until the clinical outcome from the adverse event is determined.

8.2.7. Adverse Event Reporting Period

The start of the adverse event reporting for a study subject will coincide with the day the informed consent is signed. The end of the adverse-event-reporting period occurs at the completion of study treatment or when any ongoing drug-related adverse events and/or serious adverse events have resolved or become stable. A longer reporting period applies in the case of pregnancy (see Section 8.3.2). Except as part of the long-term follow-up (see Section 7.2.16), new adverse events beginning >30 days after the last study treatment will not be considered in the safety database.

8.2.8. Site Adverse Event Reporting Requirements

Classification of an event as serious or nonserious (see Section 8.2.1.2) determines the reporting procedures to be followed. Site reporting requirements for adverse events are summarized in Table 22, below.

Table 22. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
	Within 24 hours	Fax report on designated serious adverse event report form to the INC Research Drug Safety Case Manager [a], and to the site IRB/IEC, as per local IRB/IEC requirements
	Within 5 working days	Photocopies of relevant CRFs (eg, adverse event form, medical history form, concomitant drug/therapy form) and source documents[b] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) to the INC Research Drug Safety Case Manager[a].
	Per CRF submission procedure	Record and submit information on appropriate CRFs
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs

a The INC Research Drug Safety Case Manager serious adverse event telephone number is PPD and the serious adverse event fax number is PPD
b Subject name, address, and other personal identifiers should be obscured.
Abbreviations: IRB/IEC, Institutional Review Board/Independent Ethics Committee; CRF, case report form

For serious adverse events, in addition to completing the adverse event portion of the CRF, the serious adverse event report form must also be completed. The serious adverse event report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the serious adverse event (eg, the study coordinator). The serious adverse event report form must be faxed to the contract research organization (CRO) (designated as the INC Research Drug Safety Case Manager), and to the site IRB/IEC (if required by local regulations) within 24 hours. Follow up information to the serious adverse event should be clearly documented as "follow up" in the serious adverse event report form and must be faxed to these same parties. All follow up serious adverse event report forms for the respective event must be signed by the investigator. The subject's name, address, and other personal identity information should be obscured on any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries). Only the subject's study number, initials or date of birth are to be provided. The information in the adverse event portion of the CRF page and the serious adverse event report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the adverse event.

The INC Research Drug Safety Case Manager contact information for reporting serious adverse events is:

INC Research Drug Safety Case Manager

Serious adverse event telephone number: PPD
Serious adverse event fax number: PPD

8.2.9. Study Sponsor Adverse Event Reporting Requirements

Gilead Sciences is required to expedite reports to regulatory authorities worldwide relating to serious adverse events including events related to study procedures; serious adverse drug reactions (SADRs); or suspected, unexpected, serious adverse reactions (SUSARs) consistent with relevant legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR), the European Commission Clinical Trials Directive (2001/20/EC, and revisions), and other country-specific legislation or regulations.

Each serious adverse event report received from the investigator through INC Research Pharmacovigilance will be evaluated by Gilead Sciences Drug Safety and Public Health (DSPH). Gilead Sciences DSPH will assess the seriousness of the event, the expectedness of the event, and the relationship to participation in the study. For regulatory reporting purposes, expectedness will be determined by Gilead Sciences using reference safety information specified in the investigator brochure and the event will be classified as related if either the investigator or Gilead Sciences determines that the event may be related to the study drug.

Gilead Sciences or its designee will also provide all investigators a safety letter e-mail, fax, or overnight mail notifying them of a SUSAR. Investigators will be requested to provide written notification of the SUSAR to the IRB/IEC as soon as is practical, consistent with local regulatory requirements and local institutional policy.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the Investigator's Brochure or relevant local label as applicable.

8.3. Special Situation Reporting Requirements

8.3.1. Definitions of Special Situations

Special situations include pregnancy; medication error, abuse, misuse, or overdose; and adverse reactions associated with product complaints.

- Information regarding pregnancy is provided in Section 8.3.2.
- A medication error is any preventable event that can cause or lead to inappropriate medication use or subject harm while the medication is in the control of a healthcare professional, subject, or consumer.
- Abuse is defined as persistent, sporadic or intentionally excessive use of a drug by a subject when such use is accompanied by harmful physical and/or psychological effects.

- Misuse is defined as any use of a drug in a way that is not in accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects.

- An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol (see Section 6.1.8). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excess doses or the investigator has reason to suspect that the subject has taken the additional dose(s).

- A product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

8.3.2. Pregnancy

Each female subject should be instructed to discontinue further idelalisib and inform the investigator **immediately** if she becomes pregnant at any time between the initiation of study drugs until 30 days after the last use of a study drug.

The investigator should counsel the subject regarding the possible effects of prior investigational medicinal product exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Neither the pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an adverse event; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as a serious adverse event (ie, spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting serious adverse events, ie, report the event to INC Research Pharmacovigilance by telephone and follow up by submission of the appropriate adverse event eCRFs (see Section 8.2.8).

Additional information about pregnancy outcomes that are classified as serious adverse events includes:

- Any spontaneous abortion, including miscarriage and missed abortion will be reported as a serious adverse event.

- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as a serious adverse event. The underlying medical reason for this procedure should be recorded as the adverse event term.

- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the study drug should also be reported.

- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth (ie, there is no required minimum follow-up of a presumably normal infant before the Pregnancy Outcome Report eCRF can be completed).

- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

8.3.3. Instructions for Reporting Special Situations

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on the Pregnancy Report Form and forwarded to INC Research Pharmacovigilance within 24 hours of learning of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partner of male study subjects should continue until the conclusion of the pregnancy. The outcome of the pregnancy should be reported on the Pregnancy Outcome Report Form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Sciences DSPH (facsimile: PPD
e-mail: PPD

Information regarding all other special situations must be documented on the Special Situations Report Form and forwarded to INC Research Pharmacovigilance within 24 hours of learning of the event.

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association with that situation should be reported as adverse events or serious adverse events according to the reporting requirements for those events (see Section 8.2.8). Details of signs or symptoms, clinical management, and outcome should be reported, if available.

9. WITHDRAWAL OF SUBJECTS

All study participants may receive study drug indefinitely. However:

- Any subject has the right to withdraw from the study at any time.
- Any subject who experiences progression of disease should be withdrawn from the study treatment.
- Any subject whose condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the study sponsor medical expert. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the study sponsor medical expert, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.
- Any subject who is unable to tolerate the protocol-described, dose-modified idelalisib Dose Level -1 of 100 mg BID should be withdrawn from study treatment.
- The study sponsor may discontinue the study at any time.
- If idelalisib becomes commercially available in the country where the subject is living, the study sponsor may transition subjects from study treatment to commercial drug supply (as allowed by national and local law).

The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the appropriate CRF.

When a subject is withdrawn from study treatment or is permanently removed from study treatment (regardless of the reason), all of the evaluations required at the End-of-Treatment visit should be performed and any additional evaluations should be completed that may be necessary to ensure that the subject is free of untoward effects. The subject should be encouraged to seek appropriate follow-up for any continuing health problems.

All subjects receiving ≥1 dose of study drug will be followed during the immediate post-treatment and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted.

10. STATISTICS AND DATA MANAGEMENT

10.1. Statistical Basis for Proposed Sample Size

There is no agent currently approved for use in subjects with iNHL that is refractory to both rituximab and alkylating agents. Without any therapy, the ORR for iNHL in this situation would be negligible. Off-label use of an existing agent (eg, bortezomib or lenalidomide) in this setting might be expected to yield an ORR of ~20% at the cost of considerable toxicity {Di Bella 2010, Goy 2005, Witzig 2009}. These data suggest that excluding an ORR ≤20% while targeting an ORR of ≥40% would be a conservative approach to evaluation of the idelalisib treatment effect in this population of subjects with refractory malignancy.

Accordingly, the study will test the null hypothesis that the IRC-reviewed ORR is ≤20% against the alternative hypothesis that it is ≥39% (ie, ≥~40%). Using Simon's optimum 2-stage design {Simon 1989}, a sample size of 100 subjects provides a power of >0.90 to achieve a 1-sided significance level of 0.005 and will provide an ample safety database. Under the Simon's 2-stage design, an ORR of ≥31% (ie, ≥31 subjects responding of 100 subjects evaluated) will achieve this significance level. The exact binomial test will be used in the final analyses because of the practical consideration that accrual cannot be limited to exactly 100 subjects and because subjects included in the interim analysis (see Section 10.4.1) as nonresponding may be included in the final analysis as responding if they experience a late response.

10.2. Analysis Sets

10.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will comprise all subjects who receive ≥ 1 dose of idelalisib. The ITT analysis set will be used in the analyses of ORR, PFS, OS, safety, and study drug administration and compliance. The ITT analysis set will be the primary analysis set for all the efficacy variables.

DOR and TTR will be analyzed based on all ITT subjects who achieve a CR or PR. LNR will be analyzed based on all ITT subjects who have both baseline and ≥1 evaluable post-baseline SPD.

10.2.2. Per-Protocol Analysis Set

The per-protocol (PP) analysis set will comprise all subjects in the ITT analysis set who have a diagnosis of lymphoma, who have documented refractory disease, who have measurable nodal disease as determined by the IRC, and who can be evaluated for tumor response with both a baseline and ≥1 on-study tumor evaluations. The PP analysis set will be used in analyses of ORR, DOR, TTR, LNR, PFS, and OS.

10.2.3. Pharmacodynamic/Pharmacokinetic Analysis Sets

The pharmacodynamic/pharmacokinetic (PK/PD) analysis sets include data from subjects in the ITT analysis set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

10.3. Analysis Plan

10.3.1. General Considerations

By-subject listings will be created for important variables from each CRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, standard error, 95% CIs on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, standard error, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution. Data will be summarized by visit, as appropriate for the outcome measure. Information regarding compliance with efficacy testing and data missingness will be documented. Graphical techniques (eg, waterfall plots, Kaplain-Meier curves) will be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate. Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

Analyses will be performed using SAS® (Version 9.1 or higher).

10.3.2. Subject Disposition and Characteristics

A subject listing of all treated subjects will be generated to describe site, subject number, first screening date, first treatment date, duration of treatment, analysis sets in which the subject is included (ITT, PP, PK/PD) and subject disposition. Subject disposition listings will subjectd be provided with the reasons for discontinuing treatment. A table will be created summarizing these categories in terms of number and percent for each of the populations defined above.

Subject demographic and baseline characteristics will be listed and summarized. Information regarding the diagnosis of iNHL, both as provided by the investigator and as documented by the central pathology review, will be summarized and listed.

10.3.3. Protocol Deviations

Important (major) deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be listed and summarized by deviation type.

10.3.4. Prior and Concomitant Medication Use

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary into Anatomical-Therapeutic-Chemical classification (ATC) codes. The type and timing of use of specific concomitant medications will be listed and summarized.

Descriptions of prior medication use will be focused on drugs and regimens used as treatments for iNHL. Information on the sequencing and type of prior regimens will be provided. Specific attention will be given to the details of prior rituximab and alkylator administration. In addition, details regarding response and duration of the last prior antineoplastic therapy before administration of idelalisib will be described.

Information regarding the type and use of any supportive medications (eg, antiemetics, hematopoietic growth factors) during idelalisib treatment will be described.

10.3.5. Antitumor Activity and Efficacy

Antitumor activity will be documented by radiographic response category, lymph node response rate, and the timing and duration of tumor control. SPD values, the best on-study tumor response, TTR, DOR and PFS will be listed for each subject.

Data will be presented for both investigators assessments and the IRC assessments, and the IRC assessments will be considered primary. Consistency of evaluation will be summarized by the percent agreement/disagreement between the IRC and investigator assessments.

10.3.5.1. Overall Response Rate

While the Simon optimal 2-stage design has been used to structure the trial, the exact binomial test will be used in the final analyses of ORR because of the practical consideration that accrual cannot be limited to exactly 100 subjects. The ORR and 95% CI will be presented along with the corresponding p-value from the exact binomial test.

10.3.5.2. Percent Change in Tumor Size

The LNR rate will be summarized with 95% CI based on the exact binomial distribution in the ITT and PP analysis sets using both the IRC assessments and investigators assessments. The SPD at each assessment will be described. The percent change in tumor size from baseline to each subsequent assessment will be summarized. The best percent change from baseline during the study will also be summarized. The on-treatment values will be compared with the pre-treatment baseline values using paired t-tests.

10.3.5.3. Time-to-Event Endpoints

Based on the definitions provided in Section 3.4, DOR, PFS, and OS will be described. These data will be summarized using Kaplan-Meier methods. The following censoring conventions will be applied:

- DOR and PFS: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of iNHL progression was objectively documented. Data from subjects who progress or die after ≥2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of progression was objectively documented.

- OS: Data from surviving subjects will be censored at the last time that the subject was known to be alive.

10.3.6. Health-Related Quality of Life

The FACT-Lym questionnaire (Appendix C) will be scored as recommended in the user manual for the instrument. Data for each subscale (physical well-being; social/family well-being; emotional well-being; functional well-being; additional concerns) at each assessment will be analyzed. The subscale scores, the composite scores, the individual items in B-symptoms (Fever, Night Sweats and Losing Weight) and the change scores from baseline to each subsequent assessment will be summarized. The best change from baseline during the study will also be summarized.

Data collected from the FACT-Lym instrument will not be reconciled with adverse event or laboratory data.

10.3.7. Performance Status

The Karnofsky performance status scores (Appendix D) at each assessment will be described. The change in values from baseline to each subsequent assessment will be summarized. The best and worst changes from baseline during the study will also be summarized. On-treatment values will be compared with the pre-treatment baseline values using paired t-tests.

10.3.8. Pharmacodynamic Endpoints

For each pharmacodynamic variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. The on-treatment values will be compared with the pre-treatment baseline values using paired t-tests.

10.3.9. Safety Parameters

10.3.9.1. Adverse Events

Adverse events will be classified by MedDRA using descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 3.0, whenever possible. If a CTCAE criterion does not exist, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The investigator-described relationship of the adverse event to the study drug will be categorized as ‘definite’, ‘probable’, ‘possible’, ‘unlikely’, or ‘unrelated’. Adverse events will be considered as treatment related if the causal relationship with study drug is recorded as “definite’, ‘probable’ or ‘possible’.

All adverse events will be listed. The focus of safety data summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study.

Treatment-emergent adverse events will be summarized. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. They will be presented in descending freqency by System Organ Class and then in decreasing frequency by Preferred Term.

Separate listings and summaries will be prepared for treatment-emergent adverse events classified as severe or life-threatening (Grade 3 or higher); study-drug-related adverse events; adverse events leading to treatment interruption, modification, or discontinuation; and serious adverse events.

10.3.9.2. Clinical Laboratory Tests

Sample collections will be taken either at laboratories associated with each investigational site or at laboratories that are located closer to the subject's home. However, all specimens will be sent to a central Covance laboratory for assessment.

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the period from the first dose of study drug to 30 days after the last dose of study drug. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥1 in severity) will be considered treatment-emergent. Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological, serum biochemistry, and urine data and their changes from baseline (only for continuous laboratory parameters) will be summarized by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented showing change in CTCAE severity grade from baseline to worst grade post-baseline.

For immunophenotyping data, cell count at baseline and at each assessment will be described. For immunoglobulin data, the concentrations at baseline and at each assessment will be described. Shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each visit (normal, low and high [or abnormal]). In addition, the change in values from baseline will be described at each assessment and the worst on-treatment changes during the course of the study will be computed.

10.3.9.3. Vital Signs

Vital sign data (height, weight, body temperature, systolic and diastolic blood pressures, pulse) will be obtained at each investigational site using routine clinical procedures and available equipment. Blood pressure parameters will be programmatically flagged as high or low. Systolic blood pressures ≥140 mmHg and diastolic blood pressures ≥ 90 mmHg will be classified as high, while systolic blood pressures <90 mmHg and diastolic blood pressures < 60 mmHg will be categorized as low.

Vital signs obtained during routine safety evaluations will be listed by subject and visit. Blood pressure categories will be listed by subject and visit. Vital signs and the changes from baseline for each measure will be summarized by visit. A summary of the number and percent of subjects by systolic and diastolic blood pressure category (high, normal, low) at each visit will be created.

10.3.9.4. Electrocardiography

ECG data will be generated from ECG machines at each investigational site using routine clinical procedures and available equipment. ECG data will be categorized at the investigational sites as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Standard ECG intervals will be determined. The QT interval will be corrected by both the Bazett and Fridericia method as follows:

- Bazett: $QTcB = QT/(RR)^{1/2}$
- Fridericia: $QTcF = QT/(RR)^{1/3}$

ECG data will be listed and summarized by visit. Shift tables for 12-lead ECG results (normal or abnormal) will be presented to show the change in results from baseline (normal or abnormal) to evaluations at on-treatment and end-of-treatment visits (normal or abnormal).

The QTc data obtained by using the Bazett and Fridericia corrections will be categorized separately into the following classifications and summarized by visit:

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

The change of the QTc values obtained by using the Bazett's and Fridericia's correction will also be categorized separately as follows:

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

QTc data will be presented in shift tables consistent with these categories.

10.3.10. Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of idelalisib doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

For each subject, idelalisib compliance will be described in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

10.3.11. Pharmacokinetics

Limited-sampling idelalisib plasma concentrations collected prior to the morning dose and 1.5 hours post-morning dose will be summarized by visit. Results will be placed into context with pharmacokinetics data from the Phase 1 sub-study.

10.4. Interim and Final Analyses

10.4.1. Interim Analysis

A single formal interim analysis is planned using Simon's optimal 2-stage procedure. The purpose of this interim analysis is solely to determine if there is a sufficient ORR observed early in the study to warrant continuing the study to completion. The interim analysis constitutes a futility analysis; it will not be used to stop the trial early for positive efficacy.

In Stage 1 of the study, 31 subjects will be enrolled; if ≥9 Stage 1 subjects have an OR, then the study will continue. If <9 Stage 1 subjects have an OR, accrual to the study will be halted. At the end of Stage 1, the probability of erroneously proceeding with the study is 0.151 under the null hypothesis and of erroneously discontinuing the study is 0.091 under the alternative hypothesis.

If the required Stage 1 tumor ORR is seen based on investigator assessments, accrual can proceed in Stage 2 without interruption. If the required total number of subjects are accrued to Stage 1 but follow-up is not sufficiently mature (ie, through the Week 16 radiographic evaluation) in all Stage 1 subjects to reasonably assess the Stage 1 ORR, accrual to Stage 2 may

proceed while the Stage 1 data are being collated. All available tumor response and progression data will be considered at the time of the assessment. At the latest, the interim analysis will occur when the last of the Stage 1 subjects has been enrolled and has completed the 16-week tumor assessment and these data are available for review.

10.4.2. Final Analysis

In Stage 2 of the study, it is planned that 69 subjects will be enrolled to achieve the total intended sample size of 100 subjects. The final study analysis will be performed when all enrolled subjects have completed efficacy, safety, and other assessments through ≥24 weeks of evaluation.

10.5. Data Management and Quality Assurance

The services of experienced CROs will be retained for data collection and management. Electronic data capture will be used to enter the completed CRF data into a study-specific electronic database. During the data collection process, automated quality assurance programs will be used to identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative site for resolution. CRFs will be provided to the study sponsor for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures generated by the CROs to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of the Code of Federal Regulations (CFR) Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access only to data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study sites, at the CRO, and at the study sponsor. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured in locked file cabinets when not under review.

10.6. Statistical and Data Management Rationale

The proposed sample size of 100 subjects has been established to have high power (> 90%) to exclude an uninteresting ORR of ≤20% in favor of a clinically relevant target ORR of ≥ 40%. In this calculation, the use of subjects as their own controls and omission of a contemporaneous untreated control group relies upon knowledge that, in the absence of treatment, the likelihood of achieving a ORR for subjects with iNHL refractory to rituximab and alkylating agents is extremely low (ie, has a likelihood of essentially 0%) and that even with conventionally available off-label treatments, a response rate of ≤20% is anticipated. The target ORR of ≥40% has been selected with reference to past experience with treatments for iNHL (see Section 10.1) and with consideration for the treatment effect that would likely be considered clinically meaningful.

It would have been reasonable to consider performing this trial in a single stage. However, the planned 2-stage design takes a more conservative approach by including a futility assessment. Permitting Stage 2 accrual while Stage 1 response assessment is ongoing acknowledges the high level of idelalisib activity already observed in subjects with relapsed/refractory iNHL, the well tolerated safety profile of idelalisib, and the lack of approved alternative therapies for subjects with iNHL refractory to both rituximab and alkylating agents. This plan avoids interruptions to accrual while observing initial subjects and rapidly provides a sufficiently large safety database to support of drug registration.

The proposed analytical techniques are standard and appropriate for the types of data to be assessed. Similarly, the data management methods are appropriate to assure the quality, validity, and security of the data derived from the study.

11. STUDY COMMITTEES

11.1. Study Steering Committee

A study steering committee (SSC) will be responsible for assisting the sponsor with protocol development, review of any study amendments if requested by sponsor, coordination of study conduct, interpretation of data, and presentation and publication of study results. The SSC comprises the study sponsor medical expert for the study, the study sponsor head of research and development, several clinicians with expertise in the care of subjects with iNHL and a gastroenterologist/hepatologist. Other specialists may be invited to participate as members of the SSC at any time if additional expertise is desired. Academic SSC members may be involved in accruing subjects to the study. The study sponsor medical expert serves as the chair of the SSC.

11.2. Independent Review Committee

An independent review committee (IRC) will be established to provide an objective review of radiographic data and pertinent clinical data in order to provide expert interpretation of changes in tumor status. The IRC will include independent board-certified radiologists and an independent board-certified oncologist, and will be managed by the contracted imaging core facility, BioClinica. The specifics of BioClinica's processes and reading methods will be described in an independent review charter developed by BioClinica in conjunction with the study sponsor.

12. OBLIGATIONS OF THE INVESTIGATOR AND SPONSOR

12.1. Compliance with Ethical and Regulatory Guidelines

The investigator is responsible for ensuring that the clinical study is performed in accordance with the FDA GCP regulations (CFR 21 parts 50, 56, and 312), and the International Conference on Harmonisation (ICH) GCP guidance documents.

12.2. Institutional Review Board/Institutional Ethics Committee

As required by the FDA and other regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC prior to enrollment of subjects into the study. By signing the Statement of Investigator Form (FDA Form 1572), the investigator assures that approval of the trial protocol will be obtained from the IRB/IEC and that all aspects of the IRB/IEC review will be conducted in accordance with current regulations. Amendments to the protocol will be subject to the same IRB/IEC review requirements as the original protocol. Only changes necessary to eliminate apparent immediate hazards to the subjects may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC and study sponsor in writing within 5 working days after implementation. The investigator will also promptly notify the IRB/IEC of any serious, unexpected adverse events, or any other information that may affect the safe use of the drug during the course of the trial.

A letter documenting the IRB/IEC approval and a list of the names and titles of the IRB/IEC members must be received by the study sponsor prior to the initiation of the study. All correspondence with the IRB/IEC should be retained in the investigator's study file.

The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to the study sponsor. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to the study sponsor. This report should include the dates of initiation and completion of the trial, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the trial, and the results of the trial, including a description of any adverse events. The study sponsor will assist the investigator in the preparation of this report, as needed.

If certain aspects of this study require additional IRB/IEC review, or if the study is performed under a grant from the United States government, the study sponsor will also submit the protocol and informed consent documents to the company's IRB of record. The study sponsor will be responsible for all interactions with the IRB of record, including submission of protocol documents, consent forms, and amendments; submission of adverse event reports and annual reports; receipt of approval notices; and exchange of other correspondence.

12.3. Informed Consent

By signing the Statement of Investigator (FDA Form 1572), the investigator assures that informed consent will be obtained from each subject and/or guardian prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The investigator will give each subject and/or guardian full and adequate verbal and written information regarding the objectives and procedures of the trial and the possible risks involved. An informed consent document will be provided to each subject and/or guardian in a language in which the subject or guardian is fluent. This information must be provided to the subject or guardian prior to undertaking any trial-related procedure. Adequate time should be provided for the subject and/or guardian to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject and/or guardian may have about the study. The subject should be able to ask additional questions as and when needed during the conduct of the study. The subject's signature on the informed consent form should be obtained at the investigational site in the presence of the investigator or a qualified representative (eg, sub-investigator or study coordinator) and in the presence of a witness.

Each subject or guardian will be given a copy of the signed consent/assent form. The original signed informed consent forms will be retained by the investigator with the study records.

The written subject information must not be changed without prior approval by the study sponsor and the IRB/IEC.

12.4. Case Report Forms

An electronic CRF (eCRF) is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts, or other study-specific source documents). The eCRFs exist within a Web-based electronic data capture (EDC) system managed by the data management CRO for this study. After the investigator or the investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The investigator must certify that the data are complete and accurate by signing a memo that will be sent to him by the data management CRO prior to database lock. This signature serves to attest that the information contained in the eCRFs is true. After database lock, the investigator will receive a compact disc read-only memory (CD-ROM) or paper copies of the subject data for archiving at the investigational site. At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical data entered onto the eCRFs and/or reported to the study sponsor from the investigator's site.

CRF information is the sole property of the study sponsor. Without written permission from the study sponsor, this information should not be made available in any form to third parties (except for consultants or contractors retained by the study sponsor or authorized representatives of appropriate regulatory authorities).

12.5. Study Records

During the study, the investigator will maintain adequate and complete records for the study, including the identity of all participating subjects (with sufficient information to link clinic records and eCRFs), medical records, source document records detailing the progress of the study for each subject, laboratory reports, a CD-ROM or paper copy of the data that have been captured in the EDC for each subject (electronic equivalents of CRFs), any paper CRFs, signed informed consent forms, study drug disposition records, correspondence with the IRB/IEC, adverse event reports, and information regarding subject discontinuation and completion of the study. Current regulations require the study sponsor (or an authorized designee) to inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects enrolled in this trial. These regulations also allow the same records to be inspected by authorized representatives of the FDA or other regulatory authorities.

12.6. Retention of Records and Samples

All records and documents pertaining to the study (including but not limited to those outlined in Section 12.5 above) will be maintained by the investigator until notification is received from the study sponsor that the records no longer need to be retained. This will be for a period of at least a) 2 years after approval of the drug in the United States and other countries; b) 5 years after non-approval of the New Drug Application (NDA) in the United States, Marketing Authorization Application (MAA), or a similar regulatory submission in other countries; or c) 2 years after withdrawal of the United States Investigational New Drug (IND) application or a similar regulatory permission in other countries under which this study was conducted.

The investigator must obtain written permission from the study sponsor before disposing of any records. In order to avoid any possible errors, the investigator will contact the study sponsor prior to the destruction of any study records. The investigator will promptly notify the study sponsor in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to the study sponsor.

Biological samples including tissue and blood samples collected as a study procedure or as standard of care during study participation will be stored and maintained by the investigator until notification is received from Gilead Sciences that the retained samples are no longer required. The investigator must obtain written permission from Gilead Sciences before disposing of any retained samples. The investigator should promptly notify Gilead Sciences in the event of accidental loss or destruction of any study samples. With the permission of Gilead Sciences, the retained samples may be transferred to an acceptable designee, such as another investigator, another institution, a contract storage site, or to Gilead Sciences.

12.7. Confidentiality

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs, any paper CRFs, or other records provided to or retained by the study sponsor (or its authorized designees). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by the study sponsor. The informed consent form must include appropriate statements explaining these requirements.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and the IRB/IEC will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and the IRB/IEC. By signing this protocol, the investigator affirms to the study sponsor that the investigator will maintain, in confidence, information furnished by the study sponsor and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

12.8. Financial Disclosure

As necessitated by regulation, the investigator must provide the sponsor with accurate information relating to potential financial conflicts of interest (eg, honoraria, stock ownership, inventorship, payments, etc). The sponsor will be responsible for summarizing this information and reporting it to regulatory agencies in compliance with applicable regulation.

12.9. Monitoring and Auditing

In accordance with 21 CFR 312.56 and/or relevant ICH guidelines, the study sponsor or a designee will periodically inspect all eCRFs (see Section 12.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As stipulated in Subpart D of the IND regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide the study sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, applicable FDA and other relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. At monitoring visits, the study sponsor or designee may inspect all documents and records that must be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this trial. The investigator/institution guarantees direct access to source documents by the study sponsor and appropriate regulatory authorities.

The trial site may also be subject to review by the IRB/IEC, to quality assurance audits performed by the study sponsor or a designee, and/or to inspection by the FDA and/or other regulatory authorities. The IND regulations also require the investigator to allow authorized representatives of the FDA to inspect and make copies of the same records.

It is important that the investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

12.10. Termination of the Study

The investigator reserves the right to discontinue the trial prior to inclusion of the intended number of subjects or completion of subject follow-up; the study sponsor medical expert must be notified before discontinuation of the trial by a study site. The study sponsor also reserves the right to discontinue the trial prior to inclusion of the intended number of subjects or completion of subject follow-up, but intends only to exercise this right for valid scientific or administrative reasons.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a time set by the study sponsor. As directed by the study sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

12.11. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICMJE) as a condition of consideration for publication of study results, the study sponsor will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website and that information at the website relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply the study sponsor with appropriate contact information for study site personnel.

12.12. Dissemination of Results

The information developed during the conduct of this clinical study is considered confidential by the study sponsor and must not be revealed by the investigator without permission from the sponsor.

To allow for the use of the information derived from this clinical study and to insure compliance with current regulations, the investigator is obliged to provide the study sponsor with complete test results and all data developed in this study. The study sponsor may make information obtained during this study available to further the sponsor’s scientific or business needs or as required by law or regulation. In this regard, the study sponsor may provide study information to private or public organizations (eg, business partners, collaborators, consultants, CROs, investors, other physicians who are conducting similar studies, funding organizations, regulatory authorities, or other government authorities). Such information may be publically disclosed as deemed necessary by the study sponsor.

The study sponsor intends that the data from this study will be presented and published. In collaboration with the SSC, the study sponsor staff, under the direction of the study sponsor medical expert, will be responsible for preparing presentations and writing manuscripts for publication. Investigators will not be allowed to present or publish the data from this study without prior agreement from the study sponsor.

12.13. Communication with Regulatory Authorities

The study sponsor, working either directly or through collaborators or CROs will assume responsibility for regulatory interactions with the FDA, the European Medicines Agency (EMA) and/or other regulatory authorities. The study sponsor will maintain an IND for idelalisib in support of the study in the United States and will maintain similar regulatory applications with other regulatory authorities, as required for conduct of the study. In fulfilling this responsibility, the study sponsor (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. The study sponsor (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 8.2.9.

13. RISK-BENEFIT CONSIDERATIONS

13.1. Potential Risks and Mitigating Factors

13.1.1. Potential Risks Based on Nonclinical and Clinical Idelalisib Metabolism Data

Nonclinical drug metabolism studies show that idelalisib is metabolized primarily via aldehyde oxidase, with some involvement of CYP3A. A clinical drug-drug interaction study in healthy volunteers showed that orally administered ketoconozole (a potent CYP3A inhibitor) increased idelalisib plasma exposure (AUC) 1.8-fold (Section 2.5.3), which is not considered to be clinically relevant and suggests idelalisib is a weak CYP3A substrate. Coadministration of idelalisib with rifampin, a highly potent inducer of CYP3A, resulted in ~75% lower idelalisib exposures. Coadministration of potent inducers of CYP3A with idelalisib should be avoided. Coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures, due to reversible and time-dependent inhibition of CYP3A by metabolite GS-563117. Avoid coadministration of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates, with idelalisib (see Section 6.3.6). The investigator is encouraged to contact the study sponsor medical expert to discuss specific drugs of concern.

13.1.2. Potential Risks Based on Nonclinical and Clinical Idelalisib Toxicology Data

In toxicology studies through 28 days in rats and dogs, idelalisib-related effects included lymphoid depletion (rats and dogs), bone marrow suppression (rats), and hepatotoxicity (dogs). It is possible that subjects participating in the current protocol could experience events similar to those that occurred in animals.

Mitigating the risks of similar events in humans is the knowledge that these nonclinical effects were observed at idelalisib plasma concentrations that are higher than those likely to be achieved in this study. In addition, these types of effects are readily monitored clinically and will be followed with frequent assessments of subject symptoms and laboratory parameters in the current study.

13.1.3. Potential Risks Based on Prior Clinical Experience with Idelalisib

In single-dose and 7-day multiple dose studies in healthy volunteers and in a 7-day study in subjects with allergic rhinitis, idelalisib was generally well tolerated. Healthy volunteer subjects experienced a maculopapular skin rash consistent with delayed type hypersensitivity reaction that recurred on idelalisib rechallenge. In studies evaluating prolonged administration in subjects with lymphoid malignancies, adverse events that have been considered potentially related to idelalisib have included rash, enteritis, pneumonia/pneumonitis, and elevations of serum ALT and AST. It is possible that subjects participating in the current protocol could experience events similar to those observed in prior clinical studies.

Mitigating factors are that such events have generally been recoverable or treatable. A hepatic monitoring plan has been introduced into all idelalisib protocols, including the protocol for this study. In addition, the doses and expected plasma exposures to be used in the current protocol should not exceed those evaluated in prior clinical studies. Frequent monitoring for adverse events and laboratory abnormalities is planned in the course of the current study.

13.1.4. Potential Reproductive Risks

Decreased testes weights were observed in rats and dogs, but no effect on male fertility was observed in a rat study. Changes in testicular weight in repeat dose studies are suspected to be associated with fluid production and/or tubular contraction and not a degenerative effect.

Idelalisib has induced embryo lethality and teratogenicity when administered to pregnant female rats at maternally toxic doses. However, the specific effects of idelalisib on human embryogenesis or fetal development are unknown. Whether idelalisib is excreted in human breast milk is also unknown.

Mitigating reproductive risks are that many female subjects with iNHL have lost reproductive function because they are postmenopausal or because they have received prior therapy that disrupts ovarian function; thus, this population is inherently at less risk for new adverse effects on reproductive function. Many male subjects with iNHL are beyond the age at which they are likely to conceive a child.

However, in view of the status of the current nonclinical data, measures to minimize reproductive risk are included in this study. Women of reproductive potential must have a negative serum pregnancy test and must not be breastfeeding. If a female study participant becomes pregnant or decides to breastfeed during the course of the study, idelalisib administration must be discontinued. Both women and men of reproductive potential are advised in the informed consent that they should abstain from sexual intercourse or use an adequate method of contraception throughout the duration of their participation in the trial. Study candidates are also advised in the informed consent document that the effect of idelalisib on the future ability to have children is not known.

13.1.5. General Medical Risks

It is possible that study subjects may experience new adverse events that have not already been observed in studies of idelalisib in animals or humans. It is also possible that study subjects might experience better outcomes if they elected to receive an alternative treatment rather than receiving idelalisib.

Mitigations for these types of risks are incorporated into the study design, subject eligibility criteria, idelalisib administration plan, and monitoring schedule as follows:

- Conduct of the study by expert investigators will allow consistency of methods and observation, minimizing variability that could compromise subject safety or interpretation of study data.

- Conduct of the study by qualified investigators and experienced monitors, performing the study in accordance with GCP, also enhances safety.

- The eligibility criteria are designed to identify subjects who have iNHL, are able to safely receive systemic treatment, and have the potential for therapeutic benefit.

- The planned dosing regimen is supported by safety and exposure data from completed nonclinical toxicology studies and from completed Phase 1a studies in healthy volunteers, and by evolving information from ongoing Phase 1b/2 studies of idelalisib.

- Idelalisib dose modification provisions are incorporated into the drug administration plan for subjects experiencing toxicities

- Study assessments and timing are appropriate for screening of subjects, for determination of idelalisib-related or disease-related toxicities, for dose modification during the study, for characterization of drug exposure, for evaluation of drug activity, and for assessment of tumor progression

- Appropriate guidance regarding discontinuation of subjects from study drug administration is provided to minimize harm (Section 9).

- The study investigator and the study site and study sponsor medical experts will review adverse events experienced by subjects and the study physicians will provide the appropriate treatment for these adverse events.

- The overall toxicity profile for idelalisib will be reviewed on an ongoing basis by the study sponsor, and study investigators will be updated regarding any safety issues that may be observed in other preclinical or clinical studies of idelalisib.

13.1.6. Other Potential Risks and Discomforts

During the course of the study, subjects may experience risks associated with study procedures. Such risks might include bruising, bleeding, or infection at blood collection sites; anemia; allergic reactions to radiographic contrast dye; radiation exposure during CT scanning; exposure of metallic implants to MRI-related magnetic fields; or procedure-related anxiety.

The possibilities of such risks and potential preventive measures are explained in the informed consent form. The potential risks related to radiographic procedures to be performed in the study are considered minimal, particularly in this population of subjects with iNHL who would likely undergo such testing to follow disease status even if they did not participate in the study. Subjects can be offered sedative medications to reduce procedure-related anxiety.

13.1.7. Potential Data Confidentiality Risks

As a consequence of participation in this study, medical and research records that include personal subject information will be produced. There is a risk to the subject of loss of medical confidentiality due to the existence, review, and communication of these records.

To mitigate these risks, personal identifiers will be replaced with subject numbers on study information communicated outside study sites and the link between personal identifiers and subject numbers will not be disclosed, except as required by law. Review of information containing personal identifiers will be restricted to authorized personnel from specific organizations who have responsibility to protect human subjects involved in research and to assess the validity of the data derived from this study. These organizations have been prespecified in the informed consent document. Presentation or publication of data will not include information that identifies a study subject. Measures to ensure security of study data have been incorporated into the data management plan.

13.2. Potential Benefits

The primary potential benefit to subjects participating in this clinical study is that idelalisib may induce a regression of tumors or a prolongation of PFS and/or may induce an improvement in iNHL-related symptoms. As a secondary consequence of undergoing study procedures, participants will receive a thorough review of their health status and general medical condition that may be of value to them.

Factors enhancing the potential for subject benefit are the following:

- PI3K over-expression plays an important role in iNHL biology.
- Idelalisib has been shown to impede PI3Kδ activity and to inhibit lymphoma cancer cell growth and survival in nonclinical models of lymphoid malignancy.
- At the dose level to be evaluated in this trial, idelalisib has demonstrated substantial clinical activity and positive pharmacodynamic effects in subjects with previously treated iNHL and CLL, including subjects with refractory disease and other adverse prognostic characteristics.

14. BIBLIOGRAPHY

Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol 1997;15 (4):1587-94.

Bernal A, Pastore RD, Asgary Z, Keller SA, Cesarman E, Liou HC, et al. Survival of leukemic B cells promoted by engagement of the antigen receptor. Blood 2001;98 (10):3050-7.

Brucker PS, Yost K, Cashy J, Webster K, Cella D. General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). Evaluation & the health professions 2005;28 (2):192-211.

Buske C, Hoster E, Dreyling M, Eimermacher H, Wandt H, Metzner B, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23 (1):153-61.

Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117 (19):5019-32.

Cella D, Webster K, Cashy J, Kutikova L, Burgess M, Lin BK, et al. Development of a Measure of Health-Related Quality of Life for Non-Hodgkin's Lymphoma Clinical Research: The Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) [Abstract 750]. Blood (ASH Annual Meeting Abstracts) 2005.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11 (3):570-9.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

Cheung MC, Maceachern JA, Haynes AE, Meyer RM, Imrie K. I-Tositumomab in lymphoma. Curr Oncol 2009;16 (5):32-47.

Coutre SE, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, et al. Management of adverse events associated with idelalisib treatment - expert panel opinion. Leuk Lymphoma 2015:1-20.

Crespi CM, Smith SK, Petersen L, Zimmerman S, Ganz PA. Measuring the impact of cancer: a comparison of non-Hodgkin lymphoma and breast cancer survivors. Journal of cancer survivorship : research and practice 2010;4 (1):45-58.

Di Bella N, Taetle R, Kolibaba K, Boyd T, Raju R, Barrera D, et al. Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma. Blood 2010;115 (3):475-80.

Durand CA, Hartvigsen K, Fogelstrand L, Kim S, Iritani S, Vanhaesebroeck B, et al. Phosphoinositide 3-kinase p110 delta regulates natural antibody production, marginal zone and B-1 B cell function, and autoantibody responses. J Immunol 2009;183 (9):5673-84.

Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nature reviews. Genetics 2006;7 (8):606-19.

Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46 (4):765-81.

Ferrucci L, Semba RD, Guralnik JM, Ershler WB, Bandinelli S, Patel KV, et al. Proinflammatory state, hepcidin, and anemia in older persons. Blood 2010;115 (18):3810-6.

Fisher RI, Kaminski MS, Wahl RL, Knox SJ, Zelenetz AD, Vose JM, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005;23 (30):7565-73.

Friedberg JW. Potential long-term toxicities should influence the choice of therapy for indolent non-Hodgkin's lymphoma. Haematologica 2006;91 (11):1453-5.

Friedberg JW, Cohen P, Chen L, Robinson KS, Forero-Torres A, La Casce AS, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008a;26 (2):204-10.

Friedberg JW, Mauch PM, Rimsza LM, Fisher RI. Non-Hodgkin’s lymphomas. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer: principles & practice of oncology. Philadelphia: Lippincott Williams & Wilkins; 2008b: 2098-143.

Furman RR, Byrd JC, Brown JR, Coutre SE, Benson DM, Wagner-Johnston ND, et al. CAL-101, an Isoform-Selective Inhibitor of Phosphatidylinositol 3-Kinase p110δ, Demonstrates Clinical Activity and Pharmacodynamic Effects in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia [Poster]. American Society of Hematology Meeting; 2010 December 5.

Gilead Sciences Inc. ZYDELIG® (idelalisib) tablets, for oral use. U.S. Prescribing Information. Foster City, CA. July 2014:

Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005;23 (4):667-75.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. Blood 2008;111 (12):5446-56.

Herman SE, Gordon AL, Wagner AJ, Heerema NA, Zhao W, Flynn JM, et al. Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. Blood 2010;116 (12):2078-88.

Herold M, Haas A, Srock S, Neser S, Al-Ali KH, Neubauer A, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol 2007;25 (15):1986-92.

Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106 (12):3725-32.

Horning SJ, Younes A, Jain V, Kroll S, Lucas J, Podoloff D, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J Clin Oncol 2005;23 (4):712-9.

Janikova A, Koristek Z, Vinklarkova J, Pavlik T, Sticha M, Navratil M, et al. Efficacious but insidious: a retrospective analysis of fludarabine-induced myelotoxicity using long-term culture-initiating cells in 100 follicular lymphoma patients. Exp Hematol 2009;37 (11):1266-73.

Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60 (5):277-300.

Johnston A, Bouafia-Sauvy F, Broussais-Guillaumot F, Michallet AS, Traulle C, Salles G, et al. Retreatment with rituximab in 178 patients with relapsed and refractory B-cell lymphomas: a single institution case control study. Leuk Lymphoma 2010;51 (3):399-405.

Kahl BS, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a Multicenter Study. Cancer 2010;116 (1):106-14.

Kaminski MS, Estes J, Zasadny KR, Francis IR, Ross CW, Tuck M, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood 2000;96 (4):1259-66.

Kaminski MS, Radford JA, Gregory SA, Leonard JP, Knox SJ, Kroll S, et al. Re-treatment with I-131 tositumomab in patients with non-Hodgkin's lymphoma who had previously responded to I-131 tositumomab. J Clin Oncol 2005;23 (31):7985-93.

Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2001;19 (19):3918-28.

Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:

Lannutti BJ, Meadows SA, Herman SE, Kashishian A, Steiner B, Johnson AJ, et al. CAL-101, a p110delta-selective phosphatidylinositol-3-kinase (PI3K) inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011;117 (2):591-4.

Lim ST, Hee SW, Quek R, Tao M. Performance status is the single most important prognostic factor in lymphoma patients aged greater than 75 overriding other prognostic factors such as histology. Leuk Lymphoma 2008;49 (1):149-51.

Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7 (11):1630-6.

Maloney DG, Grillo-Lopez AJ, White CA, Bodkin D, Schilder RJ, Neidhart JA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997;90 (6):2188-95.

Marcus R, Imrie K, Belch A, Cunningham D, Flores E, Catalano J, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105 (4):1417-23.

Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26 (28):4579-86.

May SE, Kashishian A, Lin TS, Jones JA, Flynn JM, Ulrich RG, et al. CAL-101, a Selective Inhibitor of the p110 Isoform of Phosphatidylinositol 3-Kinase, Effectively Induces Apoptosis in Primary Chronic Lymphocytic Leukemia Cells Providing a Novel Therapeutic Strategy for the Treatment of This Disease [Abstract 3165]. Blood (ASH Annual Meeting Abstracts) 2008;112.

McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16 (8):2825-33.

Mols F, Aaronson NK, Vingerhoets AJ, Coebergh JW, Vreugdenhil G, Lybeert ML, et al. Quality of life among long-term non-Hodgkin lymphoma survivors: a population-based study. Cancer 2007;109 (8):1659-67.

Montoto S, Davies AJ, Matthews J, Calaminici M, Norton AJ, Amess J, et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. J Clin Oncol 2007;25 (17):2426-33.

Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26 (32):5156-64.

Munk Pedersen I, Reed J. Microenvironmental interactions and survival of CLL B-cells. Leuk Lymphoma 2004;45 (12):2365-72.

Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood 2003;101 (7):2461-3.

Okkenhaug K, Bilancio A, Farjot G, Priddle H, Sancho S, Peskett E, et al. Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice. Science 2002;297 (5583):1031-4.

Okkenhaug K, Vanhaesebroeck B. PI3K-signalling in B- and T-cells: insights from gene-targeted mice. Biochemical Society transactions 2003a;31 (Pt 1):270-4.

Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. Nature reviews 2003b;3 (4):317-30.

Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013;160 (2):171-6.

Petlickovski A, Laurenti L, Li X, Marietti S, Chiusolo P, Sica S, et al. Sustained signaling through the B-cell receptor induces Mcl-1 and promotes survival of chronic lymphocytic leukemia B cells. Blood 2005;105 (12):4820-7.

Pileri SA, Zinzani PL, Went P, Pileri A, Jr., Bendandi M. Indolent lymphoma: the pathologist's viewpoint. Ann Oncol 2004;15 (1):12-8.

Piro LD, White CA, Grillo-Lopez AJ, Janakiraman N, Saven A, Beck TM, et al. Extended Rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999;10 (6):655-61.

Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma 2009;50 (5):764-72.

Reeve BB, Burke LB, Chiang YP, Clauser SB, Colpe LJ, Elias JW, et al. Enhancing measurement in health outcomes research supported by Agencies within the US Department of Health and Human Services. Qual Life Res 2007;16 Suppl 1:175-86.

Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol 2008;26 (1):132-49.

Robinson KS, Williams ME, van der Jagt RH, Cohen P, Herst JA, Tulpule A, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol 2008;26 (27):4473-9.

Salles GA. Clinical features, prognosis and treatment of follicular lymphoma. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology 2007:216-25.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol 1984;2 (3):187-93.

Schilder R, Molina A, Bartlett N, Witzig T, Gordon L, Murray J, et al. Follow-up results of a phase II study of ibritumomab tiuxetan radioimmunotherapy in patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma and mild thrombocytopenia. Cancer biotherapy & radiopharmaceuticals 2004;19 (4):478-81.

Schulz H, Bohlius JF, Trelle S, Skoetz N, Reiser M, Kober T, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007;99 (9):706-14.

Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007;110 (10):3507-16.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials 1989;10 (1):1-10.

Smith SK, Zimmerman S, Williams CS, Zebrack BJ. Health status and quality of life among non-Hodgkin lymphoma survivors. Cancer 2009;115 (14):3312-23.

Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24 (19):3187-205.

So L, Fruman DA. PI3K signalling in B- and T-lymphocytes: new developments and therapeutic advances. Biochem J 2012;442 (3):465-81.

Solal-Celigny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104 (5):1258-65.

Sujobert P, Bardet V, Cornillet-Lefebvre P, Hayflick JS, Prie N, Verdier F, et al. Essential role for the p110delta isoform in phosphoinositide 3-kinase activation and cell proliferation in acute myeloid leukemia. Blood 2005;106 (3):1063-6.

Thieblemont C, Grossoeuvre A, Houot R, Broussais-Guillaumont F, Salles G, Traulle C, et al. Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome. Ann Oncol 2008;19 (4):774-9.

Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol 2005;23 (1):10-7.

Tweats DJ, Blakey D, Heflich RH, Jacobs A, Jacobsen SD, Morita T, et al. Report of the IWGT working group on strategies and interpretation of regulatory in vivo tests I. Increases in micronucleated bone marrow cells in rodents that do not indicate genotoxic hazards. Mutat Res 2007;627 (1):78-91.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007.

van Oers MH. Rituximab maintenance therapy: a step forward in follicular lymphoma. Haematologica 2007;92 (6):826-33.

Vanhaesebroeck B, Ali K, Bilancio A, Geering B, Foukas LC. Signalling by PI3K isoforms: insights from gene-targeted mice. Trends Biochem Sci 2005;30 (4):194-204.

Victorson D, Barocas J, Song J, Cella D. Reliability across studies from the functional assessment of cancer therapy-general (FACT-G) and its subscales: a reliability generalization. Qual Life Res 2008;17 (9):1137-46.

Vidal L, Gafter-Gvili A, Leibovici L, Dreyling M, Ghielmini M, Hsu Schmitz SF, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. J Natl Cancer Inst 2009;101 (4):248-55.

Vose JM, Wahl RL, Saleh M, Rohatiner AZ, Knox SJ, Radford JA, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J Clin Oncol 2000;18 (6):1316-23.

Webb H, Chen H, Yu A, Peterman S, Holes L, Lannutti B, et al. Clinical Pharmacokinetics of CAL-101, a p1108 Isoform-selective PI3K Inhibitor, Following Single- and Multiple-Dose Administration in Healthy Volunteers and Patients with Hematological Malignancies [Abstract 1774]. ASH Annual Meeting Absracts 2010.

Wilder RB, Jones D, Tucker SL, Fuller LM, Ha CS, McLaughlin P, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. International journal of radiation oncology, biology, physics 2001;51 (5):1219-27.

Winkelmann N, Petersen I, Kiehntopf M, Fricke HJ, Hochhaus A, Wedding U. Results of comprehensive geriatric assessment effect survival in patients with malignant lymphoma. J Cancer Res Clin Oncol 2011;137 (4):733-8.

Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20 (15):3262-9.

Witzig TE, Wiernik PH, Moore T, Reeder C, Cole C, Justice G, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27 (32):5404-9.

Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980;45 (8):2220-4.

Zelenetz AD, Abramson JS, Advani RH, Andreadis CB, Byrd JC, Czuczman MS, et al. NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas. J Natl Compr Canc Netw 2010;8 (3):288-334.

Zinzani PL, Pulsoni A, Perrotti A, Soverini S, Zaja F, De Renzo A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004;22 (13):2654-61.

15. APPENDICES

Appendix A. Ann Arbor Lymphoma Staging System

Area of Involvement	Stage
Single lymph node group or lymph node region.	1
Two or more node regions on same side of diaphragm	2
Lymph node regions on both sides of the diaphragm	3
Multiple extra-nodal sites or lymph nodes and extra-nodal sites	4

Additional Anatomic Factors	Designation
Confined to lymph nodes	N
Site of bulky disease (>10 cm in diameter)	X
Extra-nodal extension or single isolated site of extra-nodal disease	E
Hepatic	H
Lung	L
Bone marrow	M
Spleen	S
Pleura	P
Bone	O
Skin	D

Additional Symptomatic Factors	Designation
No symptoms	A
Symptoms of weight loss >10% within 6 months, fever, night sweats	B

Appendix B. Follicular Lymphoma International Prognostic Index

Scoring System		
Parameter	**Value**	**Point Score**
Age	>60 years of age	1
Ann Arbor stage	Stage III or IV	1
Hemoglobin level	<120 g/L (12.0 g/dL or 6.37 mmol/L)	1
Serum LDH	>ULN	1
Number of Nodal Sites	>5	1

Risk Group by FLIPI Total Point Score	
Risk Group	**Total Point Score**
Low	≤1
Intermediate	2
High	≥3

Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal

Appendix C. Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym)

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Gs1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Appendix D. Performance Status Scoring Systems

Karnofsky and ECOG Performance Status Scoring Systems

Karnofsky Performance Status			ECOG Performances Status	
General Description	**Score**	**Specific Description**	**Score**	**Description**
Able to carry on normal activity and to work; no special care needed.	100	Normal; no complaints; no evidence of disease.	0	No symptoms, fully active, able to work.
	90	Able to carry on normal activity; minor signs or symptoms of disease.	1	Symptomatic, but not spending extra time in bed; able to do light work.
	80	Normal activity with effort; some signs or symptoms of disease.		
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.	2	In bed less than 50% of the time, unable to work, but able to care for self.
	60	Requires occasional assistance, but is able to care for most of personal needs.		
	50	Requires considerable assistance and frequent medical care.	3	In bed more than 50% of the time, though not bedridden, limited self-care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.		
	30	Severely disabled; hospital admission is indicated although death not imminent.	4	Completely bedridden
	20	Very sick; hospital admission necessary; active supportive treatment necessary.		
	10	Moribund; fatal processes progressing rapidly.		
	0	Dead		

Abbreviations: ECOG, Eastern Cooperative Oncology Group