AN OPEN-LABEL PHASE I/II SAFETY AND EFFICACY STUDY OF ITACITINIB IN COMBINATION WITH EVEROLIMUS IN SUBJECTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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LIST OF ABBREVIATIONS

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

ABVD	adriamycin-bleomycin-vinblastine-dacarbazine
ACC	Abramson Cancer Center
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
ASH	American Society of Hematology
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
AUC	area under curve
AVD	adriamycin, vinblastine, dacarbazine
BCL	B-cell lymphoma
BP	blood pressure
BUN	blood urea nitrogen
CBC	Complete Blood Count
CRF	case report form
CD	cluster of differentiation
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CNS	central nervous system
CI	confidence interval
CPK	creatine phosphokinase
CR	complete response
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSRMC	Clinical Trials Scientific Review and Monitoring Committee
CYP	cytochrome P450
DFS	disease-free survival

DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DOCM	Department of Compliance and Monitoring
DSMC	Data Safety Monitoring Committee
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
EOT	end of treatment
EMR	electronic medical record
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FLT3	FMS-like tyrosine kinase-3
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony
GVHD	graft-versus-host disease
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hCG	human chorionic gonadotropin
HDC	high-dose chemotherapy
HDL	high-density lipoprotein

HDT	high-dose chemotherapy
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HMG	3-hydroxy-3-methyl-glutaryl
HR	heart rate
HRQOL	Health-Related Quality of Life During Therapy
HRS	Hodgkin Reed-Sternberg
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IN	Investigator Notification
INCB039110	Itacitinib
INR	international normalized ratio
IPI	International Prognostic Index
IR	immediate-release
IRB	Institutional Review Board
ITT	intent to treat
IVRS	Interactive Voice Response System
IV	intravenous
HDAC	Histone deacetylases
JAK	Janus kinase
LDH	lactate dehydrogenase
LDi	longest transverse diameter of lesion
LDL	low-density lipoprotein
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities

MF	myelofibrosis
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MYD88	myeloid differentiation primary response 88
N/A	not applicable
N/D	not done
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trial
NHL	non-Hodgkin lymphoma
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NOAEL	no-observed-adverse-effect-level
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PCP	Pneumocystis pneumonia
PD	progressive disease
PET	positron emission tomography
PET/CT	positron emission tomography/computed tomography
PFS	progression free survival
Pg	prostaglandin
PgP	P-glycoprotein
PHI	protected health information
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PI3Kδ	PI3K delta isoform
PI	principal investigator
PK	pharmacokinetics
PI3K	Phosphatidylinositol 3-kinase
PO	by mouth

PR	partial response
QD	once daily
QOL	quality of life
R	rituximab
RA	rheumatoid arthritis
RP2D	recommended Phase II dose
RT	radiation therapy
SAE	serious adverse event
SCT	stem cell transplant
SOCS1	suppressor of cytokine signaling 1
SD	stable disease
SMC	Safety Monitoring Committee
SR	sustained release
STAT	signal transducer and activator of transcription
SUSAR	Suspected unexpected serious adverse reaction
T	temperature
TEAE	treatment emergent adverse event
TME	tumor microenvironment
TYK	tyrosine kinase
ULN	upper limit of normal
UPENN	University of Pennsylvania
WBC	white blood cell
WT	weight

STUDY SUMMARY

Title	AN OPEN-LABEL PHASE I/II SAFETY AND EFFICACY STUDY OF ITACITINIB IN COMBINATION WITH EVEROLIMUS IN SUBJECTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA
Short Title	Itacitinib + everolimus in HL
Trial Phase	Phase I/II
IRB Number	831774
Protocol Number	UPCC #: 45418; NCT03697408
Study Population	Subjects with relapsed/refractory classical Hodgkin lymphoma (cHL)
Rationale	While the majority of patients with classical Hodgkin lymphoma are cured, it is estimated that each year about 1000 patients will die from this disease in the United States alone. Therefore, new treatment strategies need to be developed for these patients. The molecular mechanisms underlying pathogenesis of malignant Hodgkin and Reed–Sternberg (HRS) cells are complex. It has been demonstrated that Akt, a substrate of PI3-kinase, is constitutively activated in HL-derived cell lines. Downstream effectors of Akt signaling include mTOR substrates which are also phosphorylated in HRS. Inhibitors of PI3-kinases and mTOR are clinically active in cHL as monotherapies. In a phase II trial for patients with relapsed/refractory cHL, everolimus therapy was well tolerated and resulted in response rates of about 40%, but low complete remission rate of only 5%. Everolimus is currently part of the NCCN guidelines for treatment of cHL in relapsed/refractory setting. Another pathway which is activated in HRS includes the JAK/STAT pathway which promotes tumor cell proliferation and survival. JAK inhibitor produced modest responses in patients with cHL as monotherapy. There is a rationale to combining mTOR inhibitor and JAK inhibitor in patients with cHL. In pre-clinical studies, co-treatment of mTOR inhibitor with JAK inhibitor resulted in synergistic activity against the proliferation of JAK mutated cell lines. Clinically, a study in various lymphoma subtypes using double inhibition of JAK and PI3-kinase pathway showed particular activity in cHL with ORR 60% and CR rate 20%. However, the combination was associated with pulmonary and liver toxicities and the study is currently on hold. These toxicities were attributed to the PI3-kinase inhibitor as a class.

	In our clinical trial, we plan to combine two oral agents which will target two pathways which are activated in HRS. We will administer concurrently itacinib (JAK inhibitor) with everolimus (mTOR inhibitor and a downstream effector of PI3-kinase) and hope to achieve synergistic effect without the severe toxicities observed in the PI3-kinase combination.
Design	This is an open-label, single-group, Phase I/II study of itacitinib in combination with everolimus in subjects with relapsed or refractory cHL. Phase I will evaluate the safety and tolerability of itacitinib when combined with everolimus in subjects with relapsed refractory cHL using a standard 3 + 3 design with dose-escalation or de-escalation scheme as described in Table 1; Phase II will evaluate the efficacy of the combination in subjects with cHL at the dose determined in Phase I using a Simon 2-stage optimal design. Subjects may continue to receive study treatment for a duration of 2 years (24 cycles, each cycle consisting of 28 days) or until evidence of disease progression, unacceptable toxicity, inability to commercially obtain everolimus or consent withdrawal. Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable.
Methodology	Single Center, Open-Label, Prospective Phase I/II Clinical Trial
Study Duration	Estimated duration of active enrollment is 3 years. The duration of the entire study can be up to 7 years, which would include 2 years of follow-up after the last patient completes end of treatment visit.
Objectives	**PHASE I** **Primary Objective** To evaluate dose-limiting toxicities (DLTs) of combination treatment with itacitinib and everolimus occurring up to and during Day 28 of Cycle 1, and to establish a recommended Phase II dose (RP2D) in subjects with relapsed or refractory cHL. **Secondary Objective** To evaluate efficacy of itacitinib in combination with everolimus in terms of ORR, CR, PR, SD, duration of response, PFS, OS. **Exploratory Objective** To evaluate impact of itacitinib in combination with everolimus on QOL. **PHASE II** **Primary Objective** To evaluate the efficacy of itacitinib in combination with everolimus in subjects with relapsed or refractory cHL as demonstrated by CR rate.

	Secondary Objectives To evaluate efficacy in terms of ORR, PR, SD, duration of response, PFS, OS. To evaluate the safety and tolerability of the treatment combination. **Exploratory Objective** To evaluate impact of itacitinib in combination with everolimus on QOL.
Number of Subjects	Up to 28 patients will be enrolled for planned 23 evaluable subjects
Main Inclusion and Exclusion Criteria	**MAIN INCLUSION CRITERIA:** 1. Able to understand and voluntarily sign the informed consent form. 2. Aged 18 years or older at the time of signing the informed consent form. 3. Biopsy-proven diagnosis of relapsed classical Hodgkin lymphoma. 4. Measurable disease on imaging defined as at least one lesion that can be accurately measured in at least two dimensions by imaging (PET/CT, CT, or MRI). 5. Relapsed or refractory disease (after at least 2 prior systemic therapies); patients must have relapsed after ASCT, or have been deemed ineligible for ASCT based upon the below criteria: • Patients that have either progressed after treatment with, be intolerant to, or are not a candidate for brentuximab and pembrolizumab or nivolumab. • Are not ASCT candidates due to chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy) • Advanced age (≥ 65 years of age) • Any significant coexisting medical condition likely to have a negative impact on tolerability of ASCT 6. Disease free of other malignancies for greater than or equal to 2 years. 7. Performance status of ECOG 0-2 (Appendix 13.3). 8. Laboratory test results within these ranges: • Absolute neutrophil count (ANC) > 1,000/µL • Platelet count > 75,000/µL • Serum creatinine < 2.0 mg/dL • AST and ALT ≤ 2.5 × institutional upper limit of normal (ULN) • Bilirubin < 2.0 × ULN unless due to Gilbert's disease • Fasting cholesterol ≤ 300 mg/dL AND fasting triglycerides ≤ 300 mg/dL. 9. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 72 hours prior to the first dose of itacitinib and must agree to use an effective contraception method during the study and for 6 months following the last dose of study drug.

	10. Males who have female partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drugs. 11. Subject must have access to everolimus via insurance or self-pay. **MAIN EXCLUSION CRITERIA:** 1. Unable to sign informed consent. 2. Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking the investigational agents). 3. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study. 4. Bilirubin < 3 × ULN in the presence of liver metastases or presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) 5. Concurrent use of other anti-cancer agents or therapies during study treatment. 6. Use of any other experimental drug or therapy within 28 days of initiating treatment with the investigational agents. 7. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis C (HCV), or hepatitis B virus (HBV); patients who are seropositive because of hepatitis B virus vaccine are eligible. 8. Previous use of JAK1 inhibitor (itacitinib) or history of disease progression on everolimus. 9. Has a history, within the last 12 months, of (non-infectious) pneumonitis requiring systemic steroids, or current pneumonitis.
Investigational Products	**Itacitinib** is a small molecule inhibitor of the JAK family of protein which is manufactured in 100 mg sustained release tablets and will be provided to the participants by Incyte free of charge. The starting dose of itacitinib in Phase I will be 300 mg QD (3 × 100 mg tablets); dose cohorts may be escalated to 400 mg QD or decreased to 200 mg QD depending on observed DLTs. The recommended Phase II dose identified during Phase I will be the starting dose in Phase II. Subjects may have dose reductions of itacitinib during the course of treatment based upon clinical and laboratory assessments. **Everolimus** will be administered at a dose of 5 mg QD (5 mg tablets) concurrently with itacitinib. This is an FDA approved product and part of NCCN guidelines for relapsed/refractory cHL. It will be obtained by the patient from commercial pharmacy.
Reference Therapy	None. This protocol will be given to subjects with unmet medical needs for which there are no effective therapies known at this time.

Duration of administration	Up to 2 years (24 cycles; each cycle is 28 days) of active therapy. Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable. Subjects who discontinue study treatment will be followed for disease status, subsequent anticancer treatments, and survival for up to 2 years from completing end of treatment (EOT) visit. The study will end after the last subject completes 2 year follow-up or earlier once all subjects have discontinued study treatment, all subjects have died, have withdrawn consent, or are lost to follow-up.
Statistical Methodology	**Sample size determination:** Phase I portion of the study will utilize the standard 3 + 3 design with 6 to 15 patients enrolled. At least 6 patients will need to be treated at recommended phase 2 dose (RP2D) before proceeding to Phase II. A Simon optimal 2-stage design will be implemented to rule out the null CR rate of 5% against the alternative of 25% CR rate that might lead to larger, confirmatory studies. For 80% power and 5% alpha level, the first stage will enroll up to 9 evaluable subjects. If by week 16 there are no responders from the first 9 evaluable subjects with CR, the study will be stopped. Otherwise, additional subjects will be enrolled for a total of 8-17 evaluable treated at RP2D. The study will be considered successful if 2 or more subjects achieve CR. Evaluable subject is defined as any subject who received at least 21 days of therapy and with at least one efficacy evaluation measured. **General data analysis plan:** Descriptive statistics such as mean, standard deviation, median and range for continuous variable, and percentage for categorical variables will be computed. For the safety objective, all AEs will be listed and tabulated by organ system and in CTCAE preferred terms. Point estimate of the true AE rate and 90% exact confidence intervals will be computed. For the primary efficacy objective, a two-sided 90% confidence interval will be calculated for the CR rate as well as for the ORR. Duration of response, PFS, and OS will be summarized using Kaplan-Meier curve, and median survival time will be estimated with the associated 90% CI. FACT-Lym questionnaires will assess health related QOL.
Safety Evaluations	A DLT will be defined as the occurrence of any toxicities in Table 2 occurring up to and during Day 28 of Cycle 1, except those with a clear alternative explanation (e.g., disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator and sponsor determination. All DLTs will be assessed by the investigator using CTCAE v5 criteria (NCI 2018). In order to be included in the tolerability review, subjects must have received the cohort-specific dose of itacitinib and everolimus for at least 75% of the days during the 28-day surveillance period of Cycle 1 or have experienced a

	DLT. Additional subjects may be enrolled to achieve a minimum cohort size should withdrawal or dose interruptions/reductions result in subjects being non-evaluable. The maximum tolerated DLT rate is set to be 30%. During Phase II portion of the study, a Bayesian stopping rule will be employed to monitor excess DLT rate. Under the assumption of a beta prior of (1,5), that is 1 DLT in 6 patients, the study will be stopped if 4 in 6, 5 in 9, 6 in 12, or 7 in 15 DLT are observed during cycle 1 in phase II of the study. The posterior probability that the true DLT rate is above 30% at each stopping would be around 77 to 79%. Subjects who experience a DLT or an unacceptable toxicity (i.e. not able to resume therapy within 28 days due to unresolved toxicity) beyond the DLT window will be also considered in the determination of the RP2D dose. Any grade 5 hematologic and non-hematologic event related to the study treatments (at any time) will be considered a DLT.
Data and Safety Monitoring Plan	This study will be monitored according to the Sponsor Data and Safety Monitoring Plan.

1 BACKGROUND AND STUDY RATIONALE

This document is a protocol for a human research study using itacitinib combined with everolimus in patients with relapsed or recurrent classical Hodgkin Lymphoma (cHL). This study is to be conducted according to all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1.1 Background and Relevant Literature

Classical Hodgkin lymphoma (cHL) represents 10% of all lymphomas in the U.S. with about 8,000 newly diagnosed patients each year [1]. While it is a curable malignancy for most patients, about 20% will not be cured with conventional treatments (chemotherapy, radiation). Second line therapy utilizing autologous stem cell transp4lant (ASCT) may rescue some patients with relapsed/refractory disease, but those who progress after have poor prognosis with median OS about 25 months [2]. Recent progress using immuno-conjugates or immune checkpoint inhibitors in relapsed/refractory Hodgkin lymphoma has been encouraging, but these therapies are not curative and about 1/3 of patients will not respond[3]. Furthermore, brentuximab may not be suitable for patients with neuropathy and PD-1 inhibitors may be contraindicated in those with autoimmune diseases, pneumonitis, or after allogeneic stem cell transplant. In our own practice, we have observed a growing number of young cHL patients who are progressing after these novel therapies creating a need for new treatment approaches.

The unique biology of cHL, characterized by scant Hodgkin Reed-Sternberg (HRS) cells within a pro-inflammatory tumor microenvironment (TME), is rich with therapeutic targets [4]. Constitutive activation of several signaling pathways protects HRS cells from apoptotic signals

and supports the TME, contributing to HRS cell survival, metabolism and immunity. For example, it has been demonstrated that Akt, a substrate of PI3-kinase, is constitutively activated in HL-derived cell lines. Several downstream effectors of Akt signaling, including mTOR substrates 4E-BP1 and p70 S6 kinase are also phosphorylated in HRS. In fact, everolimus, mTOR inhibitor, has been shown to be effective as monotherapy in a phase II trial for patients with relapsed/refractory cHL [5]. Nineteen heavily pretreated cHL patients were treated with 10 mg of everolimus which resulted in ORR 47% (8 PRs, 1 CR), but the CR rate was low at 5%. Overall, it was well tolerated; however, 4 patients experienced Grade 3 or higher pulmonary toxicity. There was no reported hepatotoxicity with everolimus in this study [5]. Similar clinical activity, albeit lower, was observed in a multi-center, phase II study of single-agent everolimus in the same patient population with 38 evaluable patients. The interim report demonstrated a 37% ORR (13 PRs and 1 CR) with low CR rate of 2.6% [5]. Everolimus is currently a part of NCCN guidelines as an option for patients with relapsed/refractory cHL; however, it is not currently FDA approved for this indication.

Other pathway are involved in the pathogenesis of malignant HRS cells. JAK/STAT signaling pathway activation in HRS cells has been described due to genomic amplifications or inactivating mutations in *SOCS1*, a JAK inhibitor [6]. This genomic abnormality leading to JAK/STAT activation is present in approximately 40% of HL cases [7]. JAK inhibition as monotherapy has been shown to produce modest responses with ORR 19% and no CR in 33 patients in phase II study, but the treatment was well tolerated [8]. A phase I study of SB1518 (JAK2/FLT3 inhibitor) showed that over 50% of patients with HL had stable disease after 8 weeks of daily administration. Moreover, toxicities experienced were mostly Grade 1 or 2 [9].

Concurrent inhibition of multiple activated pathways could result in enhanced activity and may represent a better strategy in HL. In pre-clinical studies, co-treatment of mTOR inhibitor with JAK inhibitor resulted in synergistic activity against the proliferation of *JAK* mutated cell lines [10, 11]. Clinically, a study in various lymphoma subtypes showed that itacitinib (JAK1 inhibitor) in combination with PI3Kδ inhibitor (INCB040093) was particularly active in HL [12, 13]. Of 6 evaluable patients receiving INCB040093, ORR was 50% (1 CR); of 9 evaluable patients receiving INCB040093 + itacitinib, ORR was 67% (2 CRs). However, there have been concerning toxicities including PCP pneumonia (in 10% of patients, but in none with cHL) and LFT elevations (about 50% of patients, mostly grade 2 or lower). These were most likely attributed to the PI3Kδ inhibitor (INCB040093) considering similar toxicities with other drugs in this class. The planned phase II trial in cHL (combining 100 mg twice daily of INCB040093 plus 300 mg of itacitinib once daily) was put on hold.

We propose to conduct a phase I/II trial using combination of itacitinib, an oral JAK1 inhibitor, with everolimus, an oral mTOR inhibitor, for patients with relapsed/refractory cHL. While both agents have activity in cHL, concurrent inhibition of both pathways in the mutation-rich HRS cells and the tumor microenvironment is more likely to result in deeper disease control (as demonstrated by CR rate) compared to everolimus monotherapy alone. We hope that combining itacitinib with everolimus (as a downstream effector of PI3-kinase) will result in synergistic effect without the toxicities seen when itacitinib was combined with PI3Kδ inhibitor (INCB040093). Both agents are oral and provide patients with convenient route of administration.

See section 10 for additional information on risk.

1.2 Description of the Investigational Products

1.2.1 Itacitinib adipate

Itacitinib adipate (referred to herein as itacitinib) is a small molecule inhibitor of the JAK family of protein TYKs with selectivity for JAK1 that is proposed for development for the treatment of MPNs, including MF; GVHD; solid tumors; B-cell malignancies; and inflammatory diseases, including RA and psoriasis. Itacitinib drug substance is a white to off-white powder. Itacitinib 100 mg (free base equivalent) sustained release tablets contain the active ingredient (itacitinib adipate), hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with MPNs and a number of chronic inflammatory conditions, and JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. Therefore, JAK inhibitors represent potential therapeutic agents for these disease states. See the itacitinib investigator's brochure for additional information.

1.2.2 Everolimus

Everolimus is an FDA approved oral agent which is labeled for several malignancies including breast cancer, lung cancer, and renal cell carcinoma. It is also part of NCCN guidelines for relapsed/refractory cHL. It potently inhibits the mammalian target of rapamycin (mTOR) blocking a key downstream effector of growth factor signaling. The functional consequences of mTOR inhibition are a rapid decline in protein translation including key glucose and amino acid transporters, resulting in a complete abrogation of extracellular nutrient uptake. Inhibition of mTOR results in cellular starvation, and everolimus is a potent initiator of metabolic stress for cancer cells. See the everolimus labeling for additional information.

1.3 Nonclinical Data

1.3.1 Itacitinib

Itacitinib did not demonstrate off-target activity or any activity in a number of non-JAK family kinases. *In vitro* studies indicate that itacitinib potently inhibits JAK1 with 22- to > 500-fold selectivity over the other JAK family members, JAK2, JAK3, and TYK2, and does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. Itacitinib is potent in cytokine-driven cell-based assays (IC_{50} values of approximately 10 nM to 350 nM). Itacitinib also inhibits the growth of the cytokine-dependent human myeloid plasma cell line, INA-6. Additional inhibition is seen for signal transducer and activator of transcription (STAT) protein phosphorylation and proinflammatory cytokines, such as interleukin (IL)-23 and IL-6 with IC_{50} values of approximately 30 nM to 100 nM. This inhibition is lessened in JAK2-dependent assays, suggesting that itacitinib is JAK2-sparing in cells (IC_{50} values of ~1 μM or greater). In JAK-dependent malignancy *in vivo* models, itacitinib continuous infusion impedes subcutaneous INA-6 expressing wild-type JAKs, achieving plasma concentrations well below those necessary to inhibit JAK2.

Single oral doses of itacitinib up to 2000 mg/kg in rats and up to 1000 mg/kg in dogs produced no adverse effects. In multiple-dose studies in rats, dose-related body weight decreases and lower food consumption were noted. Pharmacology-related alterations in the multiple-dose rat studies included reversible lowering of white blood cell (WBC) count, reversible lymphoid depletion in lymphoid tissues, and reduction in bone marrow cellularity. The no-observed-adverse-effect-level (NOAEL) in the 6-month rat study was 300 mg/kg per day. In dogs, gastrointestinal (GI) inflammation was the dose-limiting toxicity (DLT) in multiple-dose studies of up to 3 months in duration. In the 6- and 9-month dog studies, generalized demodicosis, an effect secondary to the immunosuppressive effect of itacitinib, was the DLT. The NOAEL in the 9-month study was 10 mg/kg per day.

Cytochrome P450 3A4 is the major isozyme responsible for the metabolism of itacitinib in human liver microsomes. In a cultured human hepatocyte assay, itacitinib did not induce CYP1A2, CYP2B6, or CYP3A4/5 activity or mRNA levels, suggesting that the potential to induce P450 in clinical studies is low.

Fetotoxicity and fetal malformations were observed at the highest dose levels tested when itacitinib was administered to pregnant rats and rabbits; these effects were considered secondary to severe maternal toxicity at the same dose levels.

Itacitinib lacks potential for genotoxicity as evaluated through assessments, including a bacterial reverse mutation assay, *in vitro* chromosomal aberrations study in primary human peripheral blood lymphocytes, and *in vivo* micronucleus study in rats.

Human pharmacokinetics (PK) were investigated in the Incyte trial INCB 39110-103. This was a multiple-dose, double-blind, randomized, placebo-controlled, dose escalation study in which 63 subjects were exposed orally to one of two formulation variants (SR1 or SR3) at either 200mg, 400mg, 600mg or 800mg doses in fasting and non-fasting scenarios. Steady-state PK was reached within 48 hours postdose for all the treatment groups, suggesting that the $t_{½}$ values after the first dose were likely ≤ 14 hours. Both formulations had similar mean $t_{½}$ values; 6.6 to 13 hours for SR1 (fasted or fed) and 6.5 to 8.1 hours for SR3 (fed only). Systemic accumulation was similar among the BID dose regimens; on average, geometric mean C_{max}, C_{min}, and $AUC_{0-\tau}$ increased by approximately 2-fold at the PK steady-state versus after the first dose. Additional information about itacitinib can be found in the Investigator's Brochure.

1.3.2 Everolimus

Everolimus selectively inhibits mTOR a highly conserved serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis. mTOR is the only currently known target of everolimus. mTOR is downstream of PI3K/AKT pathway, a pathway known to be dysregulated in a wide spectrum of human cancers including cHL.

Everolimus is rapidly absorbed with a median t_{max} of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen. Steady-state levels were achieved within two weeks of once daily dosing. There was no evidence of increased oncogenesis in rats and mice at 0.2 and 4.3-times, respectively, the estimated clinical exposure for Renal Cell Carcinoma patients. Additionally, in rats, everolimus was found to cross the placenta and adversely affect male

fertility at 0.5mg/kg doses and above. Accordingly, inclusion criteria require both male and female subjects to use contraception. Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of Pg. Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity.

In a recently published Phase II study of everolimus monotherapy (10mg daily, oral, 28 day cycles) in relapsed/refractory NHL, hematologic toxicity was most frequently observed (Gr 3/4 anemia (15%; 8/55), neutropenia 12%; (12/55), and thrombocytopenia (33%; 18/55); febrile neutropenia was not observed and 8/55 discontinued therapy because of adverse events. The authors concluded that everolimus monotherapy was safe and effective (ORR 35% (19/55) overall and 61% (14/23) for FL) [15]. Age, weight and gender in the adult population do not affect everolimus clearance. For more information, refer to the package insert.

1.4 Clinical Data to Date

1.4.1 Itacitinib

1.4.1.1 Monotherapy

As of December 2017, there have been 4 completed phase 1 studies and 3 ongoing study in healthy adult subjects. Studies INCB 39110-101, -102, and -103 explored the PK, safety, and preliminary pharmacology of itacitinib, and Study INCB 39110-115 evaluated the effects of itacitinib on renal function. The ongoing studies are: a Phase 1, open-label, relative bioavailability study comparing itacitinib sustained release (SR) formulations with immediate-release (IR) formulations and evaluating the effect of food on the bioavailability of these formulations (INCB 39110-105) is being conducted in healthy subjects; a Phase 1, open-label, mass-balance, PK, and metabolite profile study of radiolabeled itacitinib (INCB 39110-109); and a Phase 1, open-label, drug-drug interaction study in healthy subjects (INCB 39110-110).

In the completed clinical pharmacology studies, itacitinib was administered to 197 healthy adult subjects as a single dose, repeated single doses, or multiple doses for up to 10 days. In the ongoing bioavailability and food-effect study (INCB 39110-105), 129 subjects have been administered itacitinib SR and IR formulations. Sustained release is likely needed to maintain JAK inhibition over the dose administration interval given the relatively short half-life of IR formulation and to reduce peak-trough ratio. Of the formulations studied, the SR3 formulation was selected for expanded study because it had the greatest relative bioavailability of the SR formulations in reference to the IR formulation and had less variable PK than the other SR formulations. Additionally, the SR3 formulation may be administered without regard to food based on the least significant impact on total exposure (measured by $AUC_{0-\infty}$) compared with other formulations when administered with a medium-fat meal. An analysis of single-dose administration of itacitinib 100 mg, 200 mg, and 300 mg as SR3 100 mg tablets demonstrated that exposure increases in a greater-than-proportional manner.

In the ongoing and completed clinical pharmacology studies, itacitinib was generally safe and well-tolerated in healthy subjects, with few discontinuations. The majority of treatment-emergent adverse events (TEAEs) were mild in severity. There have been no clinically

significant, unanticipated safety findings or trends observed. The main drug effect identified was a rapidly reversible dose-related decrease in neutrophil counts presumably caused by neutrophil margination; neutrophil decreases generally resolved within 24 to 48 hours of dose discontinuation. Other reversible hematologic abnormalities, including decreased reticulocyte count, were observed after multiple-dose administration of higher dose levels at which JAK2 inhibition was noted.

See Section 5 of the itacitinib investigator's brochure for additional information.

1.4.1.2 Combination Therapies

Itacitinib has been evaluated in various combination trials in both solid and hematologic malignancies. These included combination with gemcitabine and nab-paclitaxel in subjects with advanced or metastatic solid tumors, in combination with epacadostat in solid tumors, in combination with INCB050465 (an investigational PI3Kδ inhibitor) in solid tumors, and with pembrolizumab in solid tumors.

In hematologic malignancies, itacitinib is being evaluated in combination with INCB040093, a novel phosphatidylinositol 3-kinase (PI3K) inhibitor with specificity for the delta isoform (PI3Kδ), in 2 clinical studies. As of the data cutoff date, 72 subjects with B-cell malignancies have been treated with INCB040093 in combination with itacitinib in Study INCB 40093-102. All subjects reported at least 1 TEAE. Nine subjects (12.5%) died on study; the TEAEs leading to death were hypoxia (2 subjects) and disease progression, pneumonia, Pneumocystis jirovecii pneumonia (PCP), small intestinal obstruction, death (unknown cause), cardiac arrest, and cardiorespiratory arrest (1 subject each). No DLTs have been reported. TEAEs reported in ≥ 30% of subjects included nausea, cough, fatigue, pyrexia, vomiting, chills, thrombocytopenia/platelet count decreased, and diarrhea. Treatment-related SAEs were noted for 14 subjects (19.4%) in this study; many of the treatment-related SAEs in this study were classified as infections. The most frequently reported SAE in this study was PCP (5 subjects, 6.9%) which appears to be a drug class issue for PI3K inhibitors. The use of a standard Pneumocystis prophylaxis regimen is now mandated in subjects receiving combination therapy with INCB040093 and itacitinib. Since implementing this requirement, the only case of PCP reported occurred in a subject who had previously reported PCP.

Study INCB 40093-201 is an ongoing, Phase 2, open-label study of the safety and efficacy of INCB040093, as monotherapy and in combination with itacitinib, in subjects with relapsed or refractory HL. As of the data cutoff date, 6 subjects in this study have been administered INCB040093 in combination with itacitinib. There have been no deaths or DLTs in the study. Of the 6 subjects enrolled, 4 subjects (66.7%) reported at least 1 TEAE. The most frequently reported TEAEs were nausea and vomiting (3 subjects each, 50.0%). The only SAE reported in this study was Grade 3 pyrexia for 1 subject; this event was considered to be treatment-related. Two subjects (33.3%) in this study reported TEAEs of Grade 3 or higher. No subject discontinued treatment because of a TEAE.

1.4.2 Everolimus

Everolimus has been in development for patients with cancer since 2002 and thousands of patients have been treated on various clinical trials or as part of standard of care. It is currently

FDA approved for several solid cancers metastatic renal cell carcinoma, breast cancer, neuroendocrine tumors, and unresectable lung cancer.

The clinical activity of everolimus in cHL was demonstrated in two trials as monotherapy. A phase II trial with everolimus (mTOR inhibitor) for patients with various lymphomas included 19 heavily pretreated HL patients. Everolimus showed an ORR 47%, but the CR rate was low at 5%. Although most patients experienced toxicity, the incidence of most of these complications was low and they were manageable with dose reductions. Ten patients (53%) had dose reductions or treatment delays. Adverse events at least possibly attributable to the study therapy included the following: 10 patients experienced a grade 3 or higher hematologic toxicity (six grade 3, four grade 4) and six patients experienced a grade 3 or higher non-hematologic toxicity (five grade 3, one grade 4). Grade 3 or 4 anemia, neutropenia, and thrombocytopenia occurred in 32%, 5%, and 32% of patients, respectively. Thrombocytopenia was the cause of most dose reductions and was rapidly reversible with drug delays of typically one week. Three patients had grade 3 pulmonary toxicity (two with dyspnea and one with pleural effusion) and one patient had grade 4 pulmonary toxicity (pneumonitis). There was no reported hepatotoxicity with everolimus in this study [17]. Similar clinical activity, albeit lower, was observed in a multi-center, phase II study of single-agent everolimus in the same patient population with 38 evaluable patients. The interim report demonstrated a 37% ORR (13 PRs and 1 CR) with low CR rate of 2.6% [9]. The most common hematologic AEs were thrombocytopenia (39%) and anemia (24%); the most common nonhematologic AEs were fatigue (47%), cough (29%), dyspnea (26%). Based on results of these studies, everolimus is currently a part of NCCN guidelines as an option for patients with relapsed/refractory HL.

1.5 Combination of Itacitinib and Everolimus Safety

In light of the available non-clinical and clinical information to date, the expected profile of adverse events of the combination are expected to be consistent with the individual monotherapies. Because of the potential for myelosuppression of JAK inhibitors as a class and also some of the additional myelosuppressive effects of everolimus, subjects will have hematologic parameters closely monitored during this clinical study. It is expected that the everolimus dose of 5 mg is less likely to result in prohibitive hematological toxicities. If there are clinically relevant declines in hematology parameters, investigational therapy may be interrupted until resolution or discontinuation. While hepatotoxicity was seen only for JAK inhibitor in combination with PI3Kδ, everolimus monotherapy in cHL showed no significant safety signals for liver toxicities. However, liver function tests will be monitored closely.

The 10% risk of PCP pneumonia in a study combining studies of itacitinib and PI3Kδ for various types of lymphoma was attributed to the PI3Kδ. However, considering that patients treated with everolimus had also some pulmonary toxicities (but not PCP), we plan to administer PCP prophylaxis (Appendix 13.6) and exclude any patients with history (within the past 12 months) of steroid requiring pneumonitis or active pneumonitis.

For additional information see Section 5.6

1.6 Dose Rationale for the Combination of Itacitinib and Everolimus

Both itacitinib and everolimus are metabolized by cytochrome P450 3A4 in human liver microsomes. However, in cultured human hepatocyte assays, itacitinib did not induce CYP1A2, CYP2B6, or CYP3A4/5 activity or mRNA levels, suggesting that the potential to induce P450 in clinical studies is low. The potential of itacitinib to inhibit human liver microsomal CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 activity was also investigated. The inhibitory IC_{50} values for itacitinib were > 25 μM for all isozymes, thus the potential for itacitinib to cause clinically meaningful drug-drug interactions is low.

In terms of the itacitinib, we plan to use either 200 mg, 300 mg, or 400 mg daily dose depending on tolerability and DLTs during the first Cycle 1 in Phase I patients. Steady-state PK was reached within 48 hours post-dose for all the treatment groups in healthy volunteers (i.e. 200 mg daily, 400 mg daily). Other combination trials (e.g. INCB 39110-206 of itacitinib in combination with ibrutinib in DLBCL) use a 300 mg daily starting dose of itacitinib. In light of this information, the Phase I starting dose of 300 mg was selected. Utilizing the 3+3 design and close monitoring for DLTs, we will de-escalate to 200 mg daily or escalate to 400 mg daily as per study design (Table 1). This will determine the itacitinib recommended Phase II dose (RP2D).

Everolimus will be administered at 5 mg daily at all 3 cohorts and Phase II. While two studies as monotherapy in cHL used 10 mg daily dosing, we use 5 mg daily due to the fact that 50% of patients required dose reductions or treatment delays with the 10 mg dosing (mostly due to reversible thrombocytopenia). Considering that JAK inhibitors may have also some hematologist toxicities, we decided to use 5 mg of everolimus during this combination study with itacitinib. In a study of everolimus with a multitarget tyrosine kinase inhibitor, lenvatinib, in renal cell carcinoma, the recommended phase 2 dose for everolimus was also 5 mg daily [18]. Additionally, it appears that both 5 mg daily and 10 mg daily dosing of everolimus is effective by pharmacokinetic studies and in clinical experience from the trials where dose reduction did not affect outcome [5].

2 STUDY OBJECTIVES

2.1 Phase I

2.1.1 Primary Objective

To evaluate dose-limiting toxicities (DLTs) of combination treatment with itacitinib and everolimus occurring up to and during Day 28 of Cycle 1, and to establish a recommended Phase II dose (RP2D) in subjects with relapsed or refractory cHL.

2.1.2 Secondary Objective

The secondary objective of Phase I is to evaluate the efficacy of itacitinib in combination with everolimus in terms of CR, ORR, PR, SD, duration of response, PFS, and OS.

2.1.3 Exploratory Objective

To evaluate impact of itacitinib in combination with everolimus on QOL.

2.2 Phase II

2.2.1 Primary Objective

The primary objective of Phase II is to evaluate the efficacy of itacitinib in combination with everolimus in subjects with relapsed or refractory cHL as demonstrated by CR rate.

2.2.2 Secondary Objective

The secondary objectives of Phase II are as follows:

- To evaluate efficacy in terms of ORR, PR, SD, duration of response, PFS, OS.
- To evaluate the safety and tolerability of the treatment combination.

2.2.3 Exploratory Objective

To evaluate impact of itacitinib in combination with everolimus on QOL.

3 INVESTIGATIONAL PLAN

3.1 General Design

This is an open-label, single-group, Phase I/II study of itacitinib in combination with everolimus in subjects with relapsed or refractory cHL. Phase I will evaluate the safety and tolerability of itacitinib when combined with everolimus in subjects with relapsed refractory cHL using a 3 + 3 design; Phase II will evaluate the efficacy of the combination in subjects with cHL at the dose determined in Phase I using a Simon 2-stage expansion design. Subjects may continue to receive study treatment for 2 years or until evidence of disease progression, unacceptable toxicity, inability to obtain commercial everolimus or consent withdrawal. The number of cycles may be extended if sufficient data is provided by the manufacturer demonstrating safety of the itacitinib monotherapy and the subject continues to receive a clinical benefit.

3.1.1 Screening Phase

Subjects with relapsed/refractory cHL will be recruited from the practices at the University of Pennsylvania. Subjects will not be reimbursed for participation. After signing the ICF, screening assessments may be completed over a period of up to 28 days.

3.1.2 Study Intervention Phase I

Utilizing 3 + 3 design, 6 to 15 subjects will be enrolled to Phase I portion of the trial (with at least 6 subjects treated at RP2D). The starting dose of itacitinib will be 300 mg once daily (QD) in combination with everolimus 5 mg QD. Depending on tolerability, the dose of itacitinib in combination with everolimus could be increased to 400 mg QD (Cohort 2) or decreased to 200

mg QD (Cohort -1). There will be no intra-patient dose escalations in phase I. The dose of everolimus will remain 5 mg QD for each cohort.

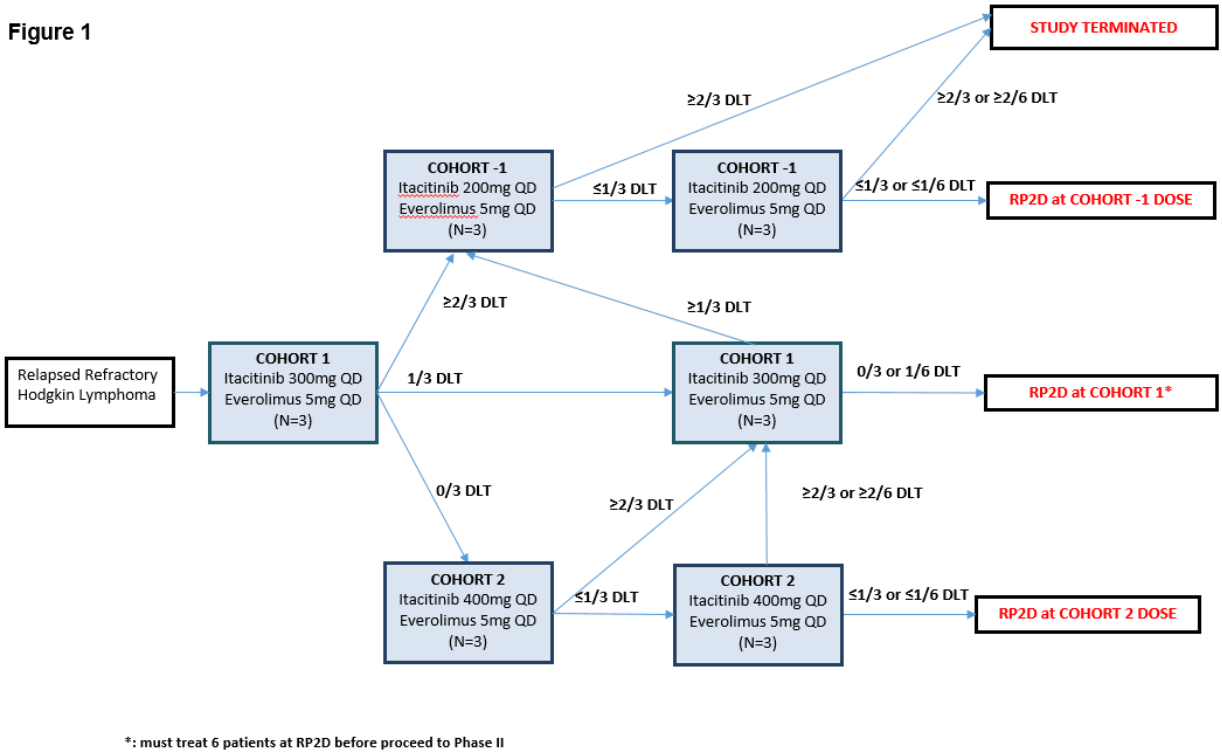
Additional subjects may be enrolled to achieve a minimum cohort size should withdrawal or dose interruptions/reductions result in a subject being non-evaluable. Dose cohorts are outlined in Table 1, and the design is depicted in Figure 1.

Subjects who experience a DLT or an unacceptable toxicity (i.e. not able to resume therapy within 28 days due to unresolved toxicity) beyond the DLT window will be also considered in the determination of the RP2D dose.

Table 1: Dose Cohort Design

Cohort	Subjects	Regimen	DLTs	Action
-1	0-6	Everolimus 5 mg QD **itacitinib 200 mg QD**	0/6	Begin Phase 2 at Cohort -1 dose
			1/3	Enroll 3 additional subjects (6 total) at Cohort -1 level; if no additional DLT, begin Phase 2 at Cohort -1 dose; if 1 or more additional DLTs, terminate study
			≥ 2	Terminate study
1 (starting dose)	3-6	Everolimus 5 mg QD **itacitinib 300 mg QD**	0/3	Escalate to Cohort 2 dose
			1/3	Enroll 3 additional subjects (6 total) at Cohort 1; if no additional DLT, begin Phase 2 at Cohort 1 dose; if 1 or more additional DLTs, de-escalate to Cohort -1
			≥ 2	De-escalate to Cohort -1
2	0-6	Everolimus 5 mg QD **itacitinib 400 mg QD**	0/6	Begin Phase 2 at Cohort 2 dose
			1/3	Enroll 3 additional subjects at Cohort 2 (6 total); if no additional DLT, begin Phase 2 study at Cohort 2 dose; if 1 or more additional DLTs, treat 3 more patients on Cohort 1 dose, if 0-1 DLTs on Cohort 1, then RP2D is Cohort 1, if ≥ 2 DLTs on Cohort 1, then de-escalate and treat 6 patients at Cohort -1; if 0-1/6 have DLTs – the RP2D is Cohort -1, if ≥ 2 DLTs, then study is terminated
			≥ 2	Treat 3 more patients on Cohort 1 dose (6 total), if 0-1 DLTs on Cohort 1, then RP2D is Cohort 1, if ≥ 2/3 DLTs on Cohort 1, then reduce to Cohort -1 and treat 6 patients. If 0-1/6 of Cohort -1 have DLTs – then RP2D is Cohort -1, if ≥ 2 DLTs, then study is terminated

Figure 1: Dose Cohort Design



3.1.3 Study Intervention Phase II

Subjects with cHL will receive the recommended Phase II dose (RP2D) of itacitinib in combination with everolimus as determined in Phase 1. Phase II will enroll 8 to 17 subjects depending on Cohort expansion in the Phase I portion. Since 6 of the Phase I subjects will be recruited, treated and followed in the same way as the Phase II subjects, they will be considered as accrued to the Phase II study as well. At least 14 subjects will be treated at RP2D level and evaluable for CR rate. Using a Simon 2-stage optimal design, if there are no responders with CR by the 16 week response assessment from the first 9 evaluable subjects at the RP2D, the null hypothesis will be considered as supported, and the study will be terminated. If there are no CRs in the first several patients (week 8 or 16 assessment), we will suspend the study enrollment and await final response assessment on all 9 patients (until week 16). The study will be considered successful if the total number of subjects with CR is ≥ 2 in Phase II.

3.1.4 Follow Up Phase

Subjects who discontinue treatment for any reason will be followed for resolution of treatment-related adverse events and survival. At treatment discontinuation, subjects will undergo a safety assessment approximately 28 days post the last dose of protocol therapy. Subjects will be

followed for additional therapy and progression/survival data every three months (+/- 1 month) for the first year and every 6 month (+/- 1 month) for the second year after study discontinuation.

3.1.5 Allocation to Interventional Group

Patients who sign ICF will be assigned a 7 digit number. First 5 digits will be the study UPCC number and the last 2 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number. During Phase I, subjects will be assigned to specific itacitinib dose Cohort as described in Table 1/Figure 1. For Phase II, subjects will be treated at the RP2D determined in Phase I.

3.2 DLT Definition

A DLT will be defined as the occurrence of any toxicities in Table 2 occurring up to and including Day 28 of Cycle 1, except those with a clear alternative explanation (e.g., disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator and sponsor determination. All DLTs will be assessed by the investigator using CTCAE v5 criteria (NCI 2018). In order to be included in the tolerability review, subjects must have received the cohort-specific dose of itacitinib and everolimus for at least 75% of the days during the 28-day surveillance period of Cycle 1 or have experienced a DLT.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug (see Section 5.6); however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the RP2D, decisions will be made based on events that are observed from the first day of study drug administration through and including Day 28. A lower RP2D may subsequently be determined based on relevant toxicities that become evident after Day 28.

Subjects who experience a DLT or an unacceptable toxicity (i.e. not able to resume therapy within 28 days due to unresolved toxicity) beyond the DLT window will be also considered in the determination of the RP2D dose.

Any grade 5 hematologic and non-hematologic event related to the study treatments (at any time) will be considered a DLT.

Table 2: DLT defining toxicities

TOXICITY
Non-hematologic
• Any ≥ Grade 3 non-hematologic toxicity, EXCEPT the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours.

– Singular or non-fasting elevations in blood glucose (i.e., blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate sequential occasions).
Hematologic
• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study drug. • Grade 4 anemia unresponsive to treatment for 3 days Note: itacitinib is suspected to cause transient decreases in ANC as a result of margination; therefore, DLT rules require neutropenia to persist after holding itacitinib for 3 days. The use of growth factors is permitted at the discretion of the investigator. If the clinical status of the subject allows, investigators are encouraged to wait 24 hours before starting growth factors, to determine if WBC margination is contributing to the degree of neutropenia.

3.3 Primary Study Endpoints

AEs will be assessed using NCI CTCAE v5.0. Efficacy endpoints will be assessed using the Lugano Classification (Appendix 13.4) (19). Duration of response will be defined as the time from earliest date of disease response until earliest date of disease progression. QOL assessment will be performed by Fact-lym questionnaires (See Appendix 13.1). The presence or absence of B symptoms (fevers over 100.4°F, drenching night sweats, weight loss of 10% of baseline weight) and of pruritus will be assessed by the research staff and recorded during study visits.

3.3.1 Phase I

3.3.1.1 Primary Phase I Endpoints

Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of AEs (including SAEs and dose-limiting toxicities [DLTs]) and changes in clinical and laboratory assessments.

3.3.1.2 Secondary Phase I Endpoints

Efficacy will be assessed by CR rate, ORR (CR and PR), clinical benefit (CR, PR and SD), and duration of response.

3.3.1.3 Exploratory Phase I Endpoints

- QOL (Fact-lym) questionnaires.
- B symptom and pruritus resolution.

3.3.2 Phase II

3.3.2.1 Primary Phase II Endpoints

- Efficacy will be assessed by CR rate, defined as the percentage of subjects achieving CR as their best response.

3.3.2.2 Secondary Phase II Endpoints

- ORR (CR and PR), clinical benefit (CR, PR and SD), and duration of response (defined as the time from earliest date of disease response until earliest date of disease progression).
- Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of AEs (including SAEs and dose-limiting toxicities [DLTs]) and changes in clinical and laboratory assessments.

3.3.2.3 Exploratory Phase II Endpoints

- QOL (Fact-lym) questionnaires.
- B symptom and pruritus resolution.

4 STUDY POPULATION AND DURATION OF PARTICIPATION

4.1 Inclusion Criteria

1. Able to understand and voluntarily sign the informed consent form.
2. Aged 18 years or older at the time of signing the informed consent form.
3. Biopsy-proven diagnosis of relapsed classical Hodgkin lymphoma.
4. Measurable disease on imaging defined as at least one lesion that can be accurately measured in at least two dimensions by imaging (PET/CT, CT or MRI). Minimum measurement must be ≥ 15mm in the longest axis or ≥ 10mm in the short axis.
5. Relapsed or refractory disease (after at least 2 prior systemic therapies); patients must have relapsed after high-dose therapy with ASCT, or have been deemed ineligible for high-dose therapy with ASCT based upon the below criteria:
   - Patients that have either progressed after treatment with, be intolerant to, or are not a candidate for brentuximab and pembrolizumab or nivolumab. The reason for forgoing such therapies must be clearly documented.
   - Are not ASCT candidates due to chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy), advanced age (≥ 65 years of age), or any significant coexisting

medical condition (renal, pulmonary, or hepatic dysfunction) likely to have a negative impact on tolerability of ASCT

6. Disease free of other malignancies for greater than or equal to 2 years with the exception of basal cell, squamous cell carcinomas of the skin, fully excised melanoma in situ, carcinoma in situ of the cervix or breast.
7. Performance status of ECOG 0-2 (Appendix 13.3).
8. Laboratory test results within these ranges (of note, patients who have cytopenias due to documented cHL involvement of the bone marrow may be considered for enrollment after discussion with the PI, Medical Director and Sponsor):
   - Absolute neutrophil count (ANC) > 1,000/µL
   - Platelet count > 75,000/µL
   - Serum creatinine < 2.0 mg/dL
   - Bilirubin < 2.0 × ULN unless bilirubin increase was due to Gilbert's disease. Further evaluation should be performed to confirm and document the origin of increase.
   - AST and ALT ≤ 2.5 × institutional upper limit of normal (ULN)
   - Fasting cholesterol ≤ 300 mg/dL AND fasting triglycerides ≤ 300 mg/dL. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication prior initiating study treatment.
9. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 72 hours prior to the first dose of itacitinib and must agree to use an effective contraception method during the study and for 6 months following the last dose of study drug; females of non-childbearing potential are those who are post-menopausal for more than 1 year or who have had a bilateral tubal ligation or hysterectomy. Female patients undergoing active fertility preservation therapy/egg harvesting which include hCG injections are expected to have mild elevation of hCG. These patients may be allowed to participate in the trial despite elevation of hCG after providing documentation of negative hCG prior the hCG injection and statement from her fertility specialist that they are not pregnant.
10. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.
11. Must be able to comply with the study and follow-up requirements.
12. Subject must have access to everolimus via insurance or self-pay.

4.2 Exclusion Criteria

1. Unable to sign informed consent form.
2. Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking the investigational agents).
3. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study. For Example:
   - symptomatic congestive heart failure of New York Heart Association Class III or IV (Appendix 13.5)
   - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
   - severely impaired lung function with O_2 saturation that is 88% or less at rest on room air
   - active (acute or chronic) or uncontrolled severe infections
   - condition requiring ongoing use of medications that are considered STRONG or MODERATE CYP3A4 inhibitors or inducers and P-gp substrates at study screening. However, those who require weak inhibitors/inducers can be enroll at discretion of the PI. See Appendix 13.2 for a list of excluded and cautionary concomitant medications.
   - liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
4. Has a history (within the past 12 months) of (non-infectious) pneumonitis requiring systemic steroids, or active pneumonitis.
5. Bilirubin < 3 × ULN in the presence of liver metastases or presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia)
6. Concurrent use of other anti-cancer agents or therapies during study treatment.
7. Use of any other experimental drug or therapy within 28 days of initiating treatment with the investigational agents.
8. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis C (HCV), or hepatitis B virus (HBV); patients who are seropositive because of hepatitis B virus vaccine are eligible.
9. Previous use of JAK1 inhibitor (itacitinib), or history of progression on everolimus.

4.3 Subject Recruitment

Subjects will be recruited from the clinical oncology practices at the Hospital of the University of Pennsylvania. Subjects will not be reimbursed for participation.

4.4 Duration of Study Participation

From enrollment, subjects will remain on active treatment for up to two (2) years, or until progression, intolerance, withdrawal of the consent, or termination of the study. Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable. Patients who, after starting this investigational combination therapy, lose the ability to obtain everolimus commercially and do not take it for duration of 28 days, will be taken off study. After end of treatment (EOT) visit, subjects will remain in follow-up for an additional two years.

4.5 Total Number of Subjects and Sites

The total planned number of evaluable subjects at UPenn will be 23 (including those in Phase I and II portions). To complete Phase I portion utilizing the 3 + 3 design, it is expected that 6 to 12 subjects will be enrolled. For phase II, 11 to 17 subjects will be enrolled. It is expected that total of 17-20 subjects will be treated at the RP2D dose since 3 to 6 patients from Phase I will be treated under the same regimen as Phase II patients. In order to be included in the tolerability review of Phase I, subjects must have received the cohort-specific dose of itacitinib and everolimus for at least 75% of the days during the first 28-day surveillance period or have experienced a DLT. Up to 5 additional subjects may be enrolled to achieve a minimum cohort size should withdrawal or dose interruptions/reductions result in subjects being non-evaluable during Phase I.

4.6 Vulnerable Populations

No vulnerable populations will be recruited.

4.7 Telemedicine Visits

To safeguard the welfare of subjects during COVID surges and/or situations that may negatively impact their safety, telemedicine visits may be utilized. The telemedicine option will be discussed with the subject prior to the scheduled visit. Visit documentation will state that the visit was conducted via telemedicine, and it will state which intervention(s) and/or assessment(s) were and were not completed. If clinically indicated, labs may be performed at an outside testing facility.

5 TREATMENT

5.1 Itacitinib

5.1.1 Description of Itacitinib

Refer to Section 1.2.1

5.1.2 Intervention Regimen

In Phase I, itacitinib tablets will be administered orally (PO) at the cohort-specific dose (Refer to Table 1/Figure 1) QD. In Phase II, itacitinib tablets will be administered PO at the RP2D identified in Phase I.

Subjects may have dose reductions of itacitinib during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 5.6.1 for itacitinib dose modification guidance.

Subjects are permitted to remain on itacitinib until withdrawal from study treatment is considered necessary or until 2 years of therapy. Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable.

5.1.3 Receipt

Itacitinib will be provided to the study team as 100 mg tablets. All Incyte investigational product labels will be in the local language and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.1.4 Storage

All itacitinib drug product should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F).

5.1.5 Preparation

No preparation is required.

5.1.6 Administration and Accountability

Itacitinib may be taken without regard to food. Due to the potential for WBC margination, blood samples should be collected before study treatment administration at all applicable study visits.

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

- Store the study medication at room temperature (15°C to 30°C, or 59°F to 86°F).
- Remove only the number of tablets from the study drug bottle needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses.
- Take study medication with a glass of water.
- Do not take another dose if vomiting occurs after taking study medication.
- Do not take study medication on the day of clinic visits until after blood samples are collected.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study medication to the site at each visit.

5.2 Everolimus

5.2.1 Description of Everolimus

Refer to Section 1.2.2

5.2.2 Intervention Regimen

In Phase I and II, everolimus tablets will be administered orally (PO) at 5 mg QD.

5.2.3 Receipt

Everolimus will be acquired by the subject from a commercial pharmacy. The subject is prescribed 28 - 5 mg tablets, packaged in a carton (typically 4 individual blister cards each containing 7 tablets for a total of 28 tablets). However, if the pharmacy has to substitute the 5 mg strength (e.g., due to a shortage), the only substitution permitted is a 2.5 mg everolimus tablet. The subject should contact the clinic at the time the pharmacy informs them of the issue.

5.2.4 Storage

Everolimus tablets must be stored in accordance with storage conditions and shelf life as indicated in the manufacturer's approved label. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

5.2.5 Preparation

No preparation is required.

5.2.6 Administration and Accountability

Subjects will be instructed on how to handle their medication. Everolimus should be administered orally once daily, preferably in the morning, at the same time as the itacitinib every day with or without food. Everolimus tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed.

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

- Store the study medication at room temperature.
- Remove only the number of tablets from the study drug blister pack as needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses.
- Take study medication with a glass of water.
- Do not take another dose if vomiting occurs after taking study medication.

- Do not take study medication on the day of clinic visits until after blood samples are collected.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study medication to the site at each visit.

5.3 Overdose

Any dose of itacitinib or everolimus in excess of that specified in this Protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate timeframe and documented as clinical sequelae to an overdose. Subjects who ingested more than the recommended dosage are instructed to immediately contact the study team and should be closely monitored and given appropriate supportive treatment.

5.4 Subject Compliance Monitoring

The subject compliance with the investigational regimen will be assessed during the scheduled visits via discussions with the subject and a count of the returned study drugs. Subjects will also be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. If subjects are determined to be non-compliant with the regimen, they may be removed from the trial at investigator discretion.

5.5 Return or Destruction of Investigational Product

Subjects will be asked to return all empty containers/blister packs and any unused study medication to each visit (see Sections 5.1.6 and 5.2.6). Unused itacitinib will be destroyed by the IDS pharmacy, when so authorized by the Sponsor. The everolimus is being dispensed through a specialty pharmacy contracted with the subject's insurance company. Study staff will adequately document pill counts and start/stop dates in the subject's EMR, but study staff will not collect or store unused everolimus that was supplied to a subject through their insurance company.

5.6 Modifications after DLT period

For subjects who are unable to tolerate the protocol-specified dosing schedule after DLT period (Cycle 1), dose adjustments are permitted in order to keep the subject on study drug for both itacitinib and everolimus. Treatment should also be delayed for major events (major events are non-treatment-related grade 3 and 4 hematologic and non-hematologic toxicities) if drug administration may further complicate the non-treatment related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ Grade 1 or ≤ baseline). For treatment-related toxicities and major events after the DLT period (for both phase I and II), if toxicity is not resolved in 4 weeks, subject will be permanently taken off study.

In a study using concurrent oral medications, it may be challenging to determine attribution especially since there may be some overlapping toxicities (e.g. cytopenias). Therefore, unless

there is a clear attribution to one of the drugs, both drugs (itacitinib and everolimus) will be held or adjusted at the same time due to adverse events according to the guidelines below in Table 3.

5.6.1 Dose Modification for Hematologic and Non-Hematologic Toxicities

Treatment with itacitinib and everolimus may be delayed up to 4 weeks (28 days) to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the Sponsor Medical Director to discuss the case of any subject whose treatment has been delayed for more than 28 days before restarting treatment with itacitinib and everolimus.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, dose interruption and reduction rules are provided as guidelines (see Table 3, Table 4, Table 5 and Table 6). Individual decisions regarding dose reduction following the DLT period should be made using clinical judgment, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 3: Guidelines for Interruption and Restarting Study Drugs due to AEs suspected to result from itacitinib or everolimus

ADVERSE EVENT	ACTION TAKEN
CHEMISTRY	
• AST and/or ALT > 3.0 × ULN or > 3.0 of the baseline if baseline was abnormal	**Step 1:** Interrupt itacitinib **and** everolimus up to 28 days until the toxicity has resolved to ≤ Grade 1 (unless approved otherwise by the medical director). **Step 2:** Restart itacitinib and everolimus at same dose, if unrelated. If assessed as related to itacitinib, restart at next lower dose. If assessed as related to everolimus, restart at next lower dose. Monitor as clinically indicated.
HEMATOLOGY	
• ANC ≤ 1.0 × 10^9/L unless due to underlying disease • Platelet count is < 60 × 10^9/L unless due to underlying disease	**Step 1:** Interrupt itacitinib **and** everolimus up to 28 days until the toxicity has resolved to ≤ Grade 1 or pre-therapy baseline. **Step 2:** Restart itacitinib **and** everolimus at same dose; monitor as clinically indicated.
• Grade 4 ANC (< 0.5 × 10^9/L) • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection. • Platelet count is < 35 × 10^9/L	**Step 1:** Interrupt itacitinib **and** everolimus up to 28 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart itacitinib **and** everolimus at same dose, if unrelated. If assessed as related to itacitinib, restart at next lower dose. If assessed as related to everolimus, restart at the next lower dose. Monitor as clinically indicated.

ADVERSE EVENT	ACTION TAKEN
OTHER	
• Any Grade 1 or Grade 2 toxicity	Continue study treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1:** Interrupt itacitinib **and/or** everolimus up to 28 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart itacitinib **and/or** everolimus at same dose if unrelated. If assessed as related to itacitinib, restart at next lower dose. If assessed as related to everolimus, restart at the next lower dose. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after dose reductions	Discontinue study itacitinib **and/or** everolimus administration. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity	Discontinue itacitinib **and/or** everolimus administration. Exceptions require approval of sponsor.

Table 4: Guidelines for Interruption and Restarting Study Drugs due to AEs suspected to result from everolimus

ADVERSE EVENT	ACTION TAKEN
Non-infectious Pneumonitis [1]	
Grade 1	No specific therapy is required Administer 100% of everolimus dose. However, depending on the clinical scenario, investigator may hold everolimus during the work-up.
Grade 2	Symptomatic only. Prescribe corticosteroids if cough is troublesome. Hold until recovery to ≤ Grade 1. Subjects will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 28 days.
Grade 3	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated. Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 28 days at a reduced dose (by one level) if evidence of clinical benefit. Subjects will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 28 days.
Grade 4	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated. Discontinue treatment.
Stomatitis [1]	
Grade 1	Use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution
Grade 2	Withhold everolimus until improvement to Grade 0 or 1. Resume at same dose. If recurs at Grade 2, withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.
Grade 3	Withhold everolimus until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.

ADVERSE EVENT	ACTION TAKEN
Grade 4	Discontinue treatment.
Hyperlipidemia	
Grade 2	Treat with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Subjects should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.
Grade 3	Withhold everolimus until improvement to Grade 0, 1, or 2. Resume at 50% of previous dose
Grade 4	Discontinue treatment.

For additional details, refer to section 5.6.2

Table 5: Guidelines for Dose Reductions for Itacitinib

Current Dose	First Dose Reduction	Second Dose Reduction
300 mg QD	200 mg QD	Discontinue
400 mg QD	300 mg QD	200 mg QD
200 mg QD	Discontinue	Discontinue

Table 6: Guidelines for Dose Reductions for Everolimus

Current Dose	First Dose Reduction	Second Dose Reduction
5 mg QD	2.5 mg QD	Discontinue
2.5 mg QD	Discontinue	Discontinue

5.6.2 Adverse Events Described with Everolimus and Management

5.6.2.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in subjects taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in subjects presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Subjects should be advised to report promptly any new or worsening respiratory symptoms.

Subjects who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration. If symptoms are

moderate (Grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a reduced dose until recovery to Grade 1 or better.

For cases where symptoms of non-infectious pneumonitis are severe (Grade 3), everolimus therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with everolimus may be re-initiated at a reduced dose depending on the individual clinical circumstances.

5.6.2.2 Hyperlipidemia and Management

Everolimus has been described to cause hyperlipidemia in some subjects. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (> 300 mg/dL) or Grade 2 hypertriglyceridemia (> 300 mg/dL) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Subjects should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual subjects based on their risk of cardiovascular complications of hyperlipidemia. See section 10 for additional information on risk.

5.6.2.3 Stomatitis and Management

Everolimus has been described to cause stomatitis/oral mucositis/mouth ulcers in some subjects. It should be treated using local supportive care.

Follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

- For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (Grade 2 in which case subjects have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case subjects cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
- Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all subjects due to their strong inhibition of everolimus metabolism,

thereby leading to higher exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6 STUDY EVALUATIONS AND PROCEDURES

6.1 Screening

The screening period is the interval between the signing of the ICF and the day that the subject is enrolled in the study (Day 1). Informed consent must be obtained before performing any study-specific procedures, but imaging from standard of care prior to screening will be acceptable for baseline tumor measurement. A subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (e.g., following recovery from an infection). Any screening studies done outside of this site's standard of care to obtain everolimus (ie any additional imaging or blood work) will be delayed until after everolimus was secured from insurance. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase:

- Review and signing of the Informed Consent Form
- Complete medical history, including prior and current medications, treatments, and anti-cancer therapies.
- Physical Exam and evaluation of ECOG PS (Appendix 13.3)
- Vital signs, including blood pressure, heart rate, oral temperature and weight
- Imaging with PET/CT scan or CT scan or MRI scan to obtain baseline tumor measurements (within 8 weeks prior to initiating study treatment)
- Complete blood count with WBC differential, serum chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT, albumin, uric acid, LDH, and erythrocyte sedimentation rate
- Viral screening tests to include testing for Hepatitis B (hepatitis B core antibody, hepatitis B surface antigen, hepatitis B surface antibody), Hepatitis C (hepatitis C antibody), HIV (HIV 1 and 2 antibody or viral load)
- Fasting lipid profile (triglycerides, total cholesterol, HDL and LDL)
- For women of childbearing potential, a serum pregnancy test must be performed within 72 hours prior to initiating treatment with itacitinib and everolimus unless the subject was undergoing egg harvesting (including hCG injections which may cause in elevated hCG levels) within 3 weeks prior to starting therapy; for those subjects, written statement from the treating fertility specialist is required to document that subject is not pregnant.

6.2 Concomitant Medications

Prior and concomitant medications and procedures will be reviewed to determine study eligibility.

Both itacitinib and everolimus are metabolized by CYP 3A4. Subjects will be instructed not to take any additional excluded medications (including over-the-counter products; see Appendix 13.2) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the subject about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The following conditions apply during the entire duration of the study:

- No other investigational therapy should be given to subjects.
- No anticancer agents other than the study medication should be given to subjects. If such agents are required for a subject then the subject must be withdrawn from the study.
- Oral contraceptives in preclinical and clinical data have shown everolimus to have CYP3A4 inhibitory activity rather than induction activity, induction of metabolism of contraceptive hormones by everolimus is unlikely. Consequently, administration of everolimus should not reduce the efficacy of oral contraceptives.
- No chronic treatment with systemic steroids (at a dose equivalent of greater than 20 mg prednisone per day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- The use of live vaccines and close contact with those who have received live vaccines should be avoided during the study treatment. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, some varicella and TY21a typhoid vaccines.
- Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus/itacitinib is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The co-administration of everolimus/itacitinib and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached.
- All subjects will be treated prophylactically with an antiviral agent (e.g., acyclovir) to prevent varicella re-activation or other viral infections

Inhibitors of CYP3A4 and/or P-gp

Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (P-gp) should be avoided. See Appendix 13.2 for detailed list of medications.

Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or P-gp inhibitors should be used with caution. If subject requires co-administration of moderate CYP3A4 inhibitors or P-gp inhibitors, reduce the dose of everolimus to half the currently used dose. If the inhibitor is discontinued the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/P-gp inhibitor.

Seville orange, star fruit, grapefruit and their juices affect P450 and P-gp activity. Concomitant use should be avoided.

See Table 7 for a summary of actions to be taken when the use of a CYP3A4/P-gp inhibitor is required.

Table 7: Recommended Dosage Modifications for Concurrent Use of a P-gp substrate or CYP3A4 Inhibitor

Type of CYP3A4 inhibitor or P-gp substrate	ACTION TAKEN
Strong Inhibitor	For temporary use – discontinue both agents (everolimus and itacitinib) until completion of inhibitor therapy. For extended use (> 28 days) – discontinue from study.
Moderate Inhibitors	Reduce treatment of both agents (everolimus and itacitinib) to 50% during treatment with moderate inhibitors.
Weak Inhibitors	Use caution. No treatment adjustments required.

Note: See appendix 13.2 for a list of CYP3A4 inhibitors and P-gp substrates

Inducers of CYP3A4 and/or P-gp

Avoid the use of strong CYP3A4 inducers. If subject requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), he or she should be removed from study. See Appendix 13.2 for detailed list of medications.

See Table 8 for a summary of actions to be taken when the use of a CYP3A4 inducer or P-gp substrate is required.

Table 8: Recommended Dosage Modifications for Concurrent Use of a P-gp substrate or CYP3A4 Inducer

Type of P-gp substrate or CYP3A4 Inducer	ACTION TAKEN
Strong Inducer	For temporary use - Use caution. No treatment adjustments required. For extended use (> 28 days) – discontinue from study.
Moderate Inducer	Use caution. No treatment adjustments required.
Weak Inducer	Use caution. No treatment adjustments required.

Note: See appendix 13.2 for a list of P-gp substrate or CYP3A4 Inducer

6.3 Diet/Activity/Other Considerations

6.3.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. They will be instructed to avoid Seville orange, star fruit, grapefruit and their juices.

6.3.2 Contraception

Everolimus and/or itacitinib may have adverse effects on a fetus in utero. Furthermore, it is not known if everolimus and/or itacitinib have transient adverse effects on the composition of sperm. Therefore while enrolled, all subjects must agree not to participate in a conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization, etc.).

Female subjects of reproductive potential (women who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure [hysterectomy or bilateral oophorectomy]) must have a negative serum or urine pregnancy test performed within 72 hours of Cycle 1/Day 1 per Table 9 Schedule of Study Procedures.

All participants participating in sexual activity that could lead to pregnancy must agree to use two methods of birth control. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm with spermicide (cannot be used in combination with cervical cap), cervical cap with spermicide (only if you have not given birth), male condom or female condom, contraceptive sponge (only if you have not given birth). Hormonal contraceptives (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection. Intrauterine Device (IUD), surgical sterility (tubal ligation or a partner that has undergone a vasectomy), or contraceptive rod implanted into the skin is also considered an acceptable method of birth control as long as a barrier method is also utilized.

Subjects may also agree to agree to completely abstain from intercourse during participation in this study and for 120 days after your last dose of study drug. Abstinence at certain times of the cycle only, such as during the days of ovulation, after ovulation and withdrawal are not acceptable methods of birth control.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement above. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.3.3 Use in Nursing Women

It is unknown whether the study drugs are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6.4 Study Intervention Phase

6.4.1 Cycle 1 Day 1

- Physical Examination and evaluation of ECOG PS (Appendix 13.3)
- Vital signs: blood pressure, heart rate, temperature, weight, oxygen saturation
- Baseline QOL FACT-lym questionnaire (Appendix 13.1; does not need to be repeated if done within 14 days prior to starting therapy)
- CBC with WBC differential and platelets (does not need to be repeated if previously performed within 3 days of starting treatment with itacitinib and everolimus)
- Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT, uric acid, LDH, and erythrocyte sedimentation rate (does not need to be repeated if previously performed within 3 days of starting treatment with itacitinib and everolimus)
- For women of childbearing potential, a serum pregnancy test must be performed within 72 hours prior to initiating treatment with itacitinib and everolimus unless the subject is actively undergoing egg harvesting (including HCG injections)

6.4.2 Cycle 1 Day 8 (+/- 3 Days)

- Physical Examination and evaluation of ECOG PS (Appendix 13.3)
- Vital signs: blood pressure, heart rate, temperature, weight, oxygen saturation
- CBC with differential and platelets (does not need to be repeated if previously performed within 24 hours before Day 8 Visit)
- Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT, uric acid, and LDH (does not need to be repeated if previously performed within 24 hours before Day 8 Visit)
- Review of interim adverse events and concomitant medications

Note: Only CBC and CMP results must be received before the subject can proceed with mediation treatment. Other test results may be received after the subject has received mediation treatment.

6.4.3 Cycle 1 Day 15 (+/- 3 Days)

- Physical Examination and evaluation of ECOG PS (Appendix 13.3)
- Vital signs: blood pressure, heart rate, temperature, weight, oxygen saturation
- CBC with differential and platelets (does not need to be repeated if previously performed within 24 hours before Day 15 Visit)
- Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT (does not need to be repeated if previously performed 24 hours before Day 15 Visit)
- Review of interim adverse events and concomitant medications
- QOL FACT-lym questionnaire (Appendix 13.1)

Note: Only CBC and CMP results must be received before the subject can proceed with mediation treatment. Other test results may be received after the subject has received mediation treatment.

6.4.4 Cycle 1 Day 22 (+/- 3 days)

- CBC with differential and platelets (does not need to be repeated if previously performed within 24 hours before Day 22 Visit)
- Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT (does not need to be repeated if previously performed 24 hours before Day 22 Visit)

6.4.5 Cycles 2-24 Day 1 (+/- 7 days)

- Physical Examination and evaluation of ECOG PS (Appendix 13.3)
- Vital signs: blood pressure, heart rate, temperature, weight, and oxygen saturation
- CBC with differential and platelets (does not need to be repeated if previously performed within 24 hours before Day 1 Visit)
- Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT, uric acid, LDH, and erythrocyte sedimentation rate (does not need to be repeated if previously performed 24 hours before Day 1 Visit)
- Review of interim adverse events and concomitant medications
- Fasting lipid profile every 2 months during active therapy (triglycerides, total cholesterol, HDL and LDL) – starting with Day 1 of Cycle 2.
- QOL FACT-lym questionnaire (Appendix 13.1)

Note: Only CBC and CMP results must be received before the subject can proceed with mediation treatment. Other test results may be received after the subject has received mediation treatment.

Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable. During these additional cycles, the same assessments will be captured as cycles 4-24.

In the event that a telemedicine visit is conducted, the following tests will be postponed until the next in-person visit:

- Physical examination
- Vital Signs
- Return of IP
- Fact-lym QOL questionnaire

6.4.6 End of Treatment Visit (EOT)

The following will be performed at the time of study discontinuation, whether due to study completion or early withdrawal from study participation. This visit should occur within 28 days from the last dosing:

- Physical Exam and evaluation of ECOG PS (Appendix 13.3)
- Vital signs (Blood pressure, heart rate, temperature, weight, oxygen saturation)
- CBC with differential and platelets
- Serum chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT, uric acid, LDH, and erythrocyte sedimentation rate
- Fasting lipid profile
- Serum pregnancy test (women of child-bearing potential)
- Assessment of adverse events and concomitant medications
- QOL FACT-lym questionnaire (Appendix 13.1)

6.4.7 Safety Assessments

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 28 days (+/- 7 days) after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported as

described in section 8.3. Reasonable effort should be made to have the subject return for the follow-up visit and report any AEs that may occur during this phase.

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

6.4.8 Follow-up Phase

6.4.8.1 Follow-up Period for Disease Status

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period for 2 years from the EOT visit. They should be assessed at least every 3 months (+/- 30 Days) using physical exam and standard of care blood work (CBC with diff, Serum Chemistry panel including sodium, potassium, chloride, CO_2, calcium, serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT,) during the first year and every 6 months (+/- 30 Days) for the second year. The follow-up portion of the study will end at 2 years from the EOT of the last subject or earlier once all subjects have discontinued study treatment, and all subjects have died, have withdrawn consent, or are lost to follow-up.

The imaging frequency will be at the discretion of the treating physician, but at least every 6 months (+/- 1 month) to monitor disease status during the first 2 years after EOT. Every effort should be made to collect information regarding disease status until:

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

Patients who undergo HDT/allogeneic SCT within one year of completing study treatment will be followed for one year after the transplant, in order to collect data from the following events: GVHD, pulmonary complications, hepatic veno-occlusive disease, immune-mediated AEs, critical illness, and transplant-related mortality.

6.4.8.2 Follow-up for Survival Status

Once a subject has confirmed disease progression, or starts a new anticancer therapy, the subject moves into the survival follow-up period. The subject should then be contacted by telephone, email, visit, or by review of the subject's EMR at least every 12 weeks, according to the tables below, to assess for survival status. Subject will remain enrolled until completion of follow-up, death, withdrawal of consent, or the end of the study, whichever occurs first.

Disease Follow-Up Phase (for subjects with non-disease progression)

	EOT + 28 days	EOT + 3 mo.	EOT + 6 mo.	EOT + 9 mo.	EOT +12 mo.	EOT + 18 mo.	EOT + 24 mo.
Physical		X	X	X	X	X	X
Labs*		X	X	X	X	X	X
All AEs**	X						
Imaging			X		X	X	X

* CBC with diff, serum chemistry panel including sodium, potassium, chloride, CO2, calcium serum creatinine, BUN, total bilirubin, alkaline phosphatase, AST, ALT
** Related AEs should be followed until resolution, lost to follow up, or judged to be permanent

Survival Follow-Up Phase (for subjects with disease progression or those who have started a new anticancer therapy)

	EOT* + 28 days	EOT + 12 wks.	EOT + 24 wks.	EOT + 36 wks.	EOT + 48 wks.**
All AEs***	X				
Check survival****		X	X	X	X

* Survival Follow-Up starts at EOT if PD, or if not PD, then when a new anticancer therapy starts
** Every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.
*** Related AEs should be followed until resolution, lost to follow up, or judged to be permanent
**** By telephone, email, visit, or review of EMR

6.5 Physical Examination

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or a certified registered nurse practitioner.

The physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; lungs; cardiovascular system; abdomen; extremities; lymph nodes.

6.6 Laboratory Assessment

Specific laboratory assessments are listed in Table 9. The total amount of blood to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn/collected by visit and by sample type per subject may vary depending upon clinical course of the subject and length of time on trial. Blood draws will be completed before the subject receives the morning dose of itacitinib. Subjects will be allowed to have lab work performed at external labs in the event that a study visit is conducted remotely, if clinically indicated.

6.7 Radiographic Evaluations

Subjects will undergo radiographic evaluations to assess disease status at the time points listed below. Timing of radiographic evaluations may be altered based on clinical indication or the discretion of the treating physician.

- Baseline imaging (preferably with FDG-PET/CT, but CT C/A/P or MRI C/A/P are also acceptable) within 8 weeks of starting therapy.
- If imaging was performed as standard of care before signing of the ICF but within 8 weeks of Day 1, then the results from that assessment may be recorded in the eCRF in lieu of a study-specific assessment.
- Response assessment with imaging (investigator choice depending on clinical situation) at week 8 and 16 during the first 4 months of active therapy and every 16 weeks for the remaining active treatment period.
- Imaging will be performed at least every 6 months during the 2 year follow-up period after EOT for patients who came off study for reasons other than progression and who did not start another therapy.

6.8 Unscheduled Visits

An unscheduled visit can occur at any time during the study. The date for the visit and any data (i.e. recording of new AEs) generated must be recorded in subject's chart.

6.9 Subject Withdrawal

6.9.1 Treatment Discontinuation

A subject may be discontinued from treatment regimen using itacitinib and everolimus prior to the expected completion for disease progression, failure to adhere to protocol requirements, failure to obtain everolimus or if the investigator or subject deems it in the subject's best interest to discontinue. The reason justifying study treatment discontinuation should be documented in the study records. Subjects who discontinue the study regimen prior to completion will remain on study for follow-up, unless they withdraw consent. All subjects who receive at least 1 dose of study drug will be followed for toxicity, response and survival unless they withdraw consent.

A subject may be withdrawn from the study (during treatment or follow-up) for reasons including death, subject withdrawal of consent for further follow-up, if the subject is lost to follow-up, or at study termination by study sponsor or by Incyte (drug manufacturer/funding sponsor). If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate the subject should be terminated, an appropriate schedule for termination will be instituted. All subjects who are terminated will complete EOT visit (see section 6.4.6).

The investigator retains the right to terminate his participation in the study at any time. Should this occur, the investigator is to notify the Sponsor in writing.

The sponsor may terminate the study electively or if required by regulatory decision (e.g., FDA request). If the study is terminated prematurely, the sponsor will notify the investigators, the IRB and regulatory bodies of the decision and reason for termination of the study.

Table 9: Schedule of Study Procedures

Study Phase	Screening	Cycle 1				Cycles 2-24[d, p]	EOT[l]	Disease Follow-up	Survival Follow-up
Study Days	**Day -28 to -1**	**Day 1**	**Day 8 ±3**	**Day 15 ±3**	**Day 22 ±3**	**Day 1 ±7**			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6 - 30**	**31**		
Informed Consent	X								
Review Inclusion/Exclusion Criteria	X								
Demographics/Medical History	X								
ECOG PS	X	X	X	X		X	X		
FACT-lym questionnaire		X[j]		X		X[q]	X		
Physical Examination	X	X	X	X		X[q]	X	X[f]	
Vital Signs: BP, HR, T, WT, O_2 Saturation	X	X	X	X		X[q]	X		
Height	X								
Pregnancy Test[c]	X						X		
Prior/Concomitant Medications	X	X	X	X			X		
Confirm that PCP prophylaxis was started[k]		X							
Clinical Laboratory Evaluation[a,b, i, m,]	X	X[n]	X[g]	X[g]	X[g]	X[h, n, q]	X	X[f]	
Antiviral Medication[o]	X								
Cohort Assignment (Phase I)		X							
Dispense Investigational Product		X				X[r]			
Everolimus Availability by Subject	X								
Adverse Event Assessment			X	X		X	X		
Assess drug compliance/subject's study calendar			X	X		X	X		
Imaging[d]	X					X[q]	X	X[e]	
Follow-up anti-cancer treatments									X

[a] Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

[b] Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, uric acid, LDH, erythrocyte sedimentation rate, and fasting lipid panel. Uric acid and LDH shall be performed during Screening, Cycle 1 Day 1, Cycle 1 Day 8, Day 1 of Cycle 2 through Cycle 24, and EOT. Erythrocyte sedimentation rate shall be performed during Screening, Day 1 of Cycle 1, Day 1 of Cycle 2 through Cycle 24, and EOT. The fasting lipid panel will be drawn only on screening and Day 1 of every 2 cycles (starting with Day 1 Cycle 2).

[c] A serum pregnancy test will be performed at screening and EOT. Urine pregnancy test will be performed only if pregnancy is suspected during treatment; positive results must be confirmed with a serum pregnancy test. Pregnancy testing will only be required for women of childbearing potential.

[d] Baseline imaging (preferably with FDG-PET/CT, but CT C/A/P or MRI C/A/P are also acceptable) within 8 weeks of starting therapy. If imaging was performed as standard of care before signing of the ICF but within 8 weeks of Day 1 Cycle 1, then the results from that assessment may be recorded in the eCRF in lieu of a study-specific assessment. Response assessment with imaging (investigator choice depending on clinical situation) at week 8 and 16 during the first 4 months of active therapy and every 16 weeks for the remaining active treatment period. Timing of each imaging is acceptable within +/- 1 week of the protocol specified during first 4 months of therapy and +/- 2 weeks during the remaining active treatment period.

[e] Imaging will be performed at least every 6 months during the 2 year follow-up period after EOT and then at the discretion of the treating physician.

[f] In disease follow-up phase – subjects who discontinue study treatment for a reason other than disease progression will be followed-up for 2 years from EOT. They should be assessed at least every 3 months (+/- 1 month) using physical exam and standard of care blood work during the first year and every 6 months (+/- 1 month) for the second year. Imaging will be done every 6 months (+/- 1 month) during the 2 years of follow-up.

[g] Plus/minus 3 days

[h] Plus/minus 7 days

[i] Viral screening tests to include testing for Hepatitis B (hepatitis B core antibody, hepatitis B surface antigen, hepatitis B surface antibody). Hepatitis C (hepatitis C antibody), HIV (HIV 1 and 2 antibody or viral load)

[j] Does not need to be repeated if done within 14 days prior starting study treatment

[k] PCP prophylaxis (see appendix 13.6 for options) will start before or at Day 1 Cycle 1 and continue until EOT visit.

[l] EOT visit should occur within 28 days of last dosing.

[m] Results may be obtained up to 3 days prior to treatment.

[n] CBC and CMP results must be received before the subject can proceed with mediation treatment.

[o] Antiviral medication to be taken for the duration of the active trial treatment

[p] Additional cycles of investigational treatment may be added if in the opinion of the investigator that the benefit risk ratio for the subject continues to be favorable.

[q] Not performed when visit is via telemedicine. If clinically indicated, labs may be performed at an outside testing facility.

[r] Study medicine will be shipped directly to subject when a telemedicine visit occurs.

7 STATISTICAL PLAN

7.1 Sample size

Sample size determination: Utilizing 3 + 3 design, 6 to 15 subjects will be enrolled to Phase I portion of the trial (with at least 6 subjects treated at RP2D). Phase II will enroll 8 to 17 subjects depending on expansion needs in the Phase I portion. At least 14 subjects will be treated at RP2D level and evaluable for CR rate. The sample size for phase II was based on a decision between 2 pre-specified hypotheses about the probability of CR rate (p). The null hypothesis H_0: p = 5% reflects a response rate that would be of no clinical benefit compared to everolimus alone, and the alternative hypothesis H_a: p = 25% is a CR rate that might lead to larger, confirmatory studies. Using a Simon 2-stage optimal design, a total of 17 subjects at RP2D will be needed for 80% power at 1-sided alpha = 0.05 level. If by the 16 week visit there are no responders with CR from the first 9 evaluable subjects (at any itacitinib dose level), the null hypothesis will be considered as supported, and the study will be terminated.

7.2 Statistical Methods

Time to event data including OS, PFS, DOR will be analyzed using Kaplan-Meier method, treating subjects with no observed death as censored at their last date known to be alive for OS or last documented tumor measurement for PFS and DOR. Median survival and 90% CI will be estimated. Overall survival data will continue to be collected until 75% of subjects have died, have withdrawn consent, or are lost to follow-up.

7.2.1 Interim Efficacy Analysis

The efficacy analysis is based on Simon 2 stage optimal design and will be performed after the enrollment of the first 9 evaluable subjects. If there are no responders with CR from the first 9 evaluable subjects (at the 8 week or 16 week response assessment, at any itacitinib dose level), the null hypothesis (CR rate of 5% or lower with the new combination) will be considered as supported, and the study will be terminated. If there are no CRs in the first three (3) patients (week 8 or 16), we will suspend the study enrollment and await final response assessment on all 9 patients (6 in Phase I and 3 in Phase II). The study will be considered successful if the total number of subjects with CR is ≥ 2 in Phase II (at the 8 week or 16 week response assessment).

7.2.2 Interim Safety Analyses

The safety analysis is based on Bayesian probability calculations and will be performed after the first 6 subjects treated at the RP2D and then after enrollment of 9, 12, and 15 subjects at RP2D dose. The max tolerated DLT (see section 3.2) rate is 30% and a beta prior of (1,5) is assumed (that is 1 DLT in 6 subjects). The study will be terminated if 4 DLTs in 6 subjects, 5 in 9, 6 in 12, or 7 in 15 are observed. The posterior probability that the true DLT rate is above 30% at each stopping would be around 77 to 79% (79%, 78%, 78%, and 77% respectively).

If there are two (2) study related deaths in the phase I portion, the study will be terminated.

7.3 Subject Population for Analysis – Phase I

In order to be included in the tolerability review, a subject must have received the cohort-specific dose of itacitinib and everolimus for at least 75% of the days during the 28-day DLT surveillance period or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size of 3-6 (see Figure 1) should withdrawal or dose interruptions/reductions result in a subject being non-evaluable. Subjects who receive at least one dose of the combined treatment (itacitinib and everolimus) will be assessed for adverse events, response, survival and exploratory analyses (FACT-lym, resolution of B symptoms or pruritus).

7.4 Primary Analyses

The primary endpoint of Phase I is safety and tolerability by evaluating the frequency, duration, and severity of AEs as assessed by the investigators using CTCAE v5.0 criteria. The primary endpoint of Phase II is CR rate; a subject will be considered as a complete responder if his or her best overall response is CR on the Lugano Classification (Appendix 13.4) (Cheson et al 2014). The rate of responders will be estimated together with 90% confidence interval (CI). The study will be considered successful if the total number of complete responders is ≥ 2 in Phase II.

7.5 Secondary Analyses

Lugano Classification (Appendix 13.4) (19) will be used to evaluate efficacy in terms of ORR, CR, PR, SD. Progression-free survival (PFS) will be determined from the enrollment date until the earliest date of disease progression, as measured by investigator assessment of objective radiographic disease assessments per Lugano Classification, or death due to any cause if earlier. Progression-free survival data will be analyzed using Kaplan-Meier method, treating subjects with no observed death or progression as censored at the last valid radiologic assessment visit. Median PFS and 90% CI will be estimated.

Overall survival (OS) will be determined from the enrollment date until death. Survival data will be analyzed using Kaplan-Meier method, treating subjects with no observed death as censored at their last date known to be alive. Median survival and 90% CI will be estimated. Overall survival data will continue to be collected until 75% of subjects have died, have withdrawn consent, or are lost to follow-up.

The DOR is defined as the difference of the end of response and the start of response for subjects who have achieved a response. The start of a response will be the first visit where the subject achieves PR or better based on the Lugano Classification. The end of response will be the first visit where PD is assessed based on the Lugano Classification. Duration of response will be assessed using Kaplan-Meier method for subjects who achieve a response. Median duration and 90% CI will be estimated. Subjects who are still responding at the time of database freeze or discontinuation will be censored at the last valid radiologic assessment visit.

7.6 Other Analyses

Exploratory end points include exploration of health-related quality of life during therapy (HRQOL) using The FACT-lym questionnaire. This has been validated in subjects with various forms of lymphoma. It contains 42 items (questions) covering HRQOL and common lymphoma

symptoms and treatment side-effects. The questionnaire begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 items covering four core HRQOL subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items), addressing issues typically experienced by lymphoma subjects. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. The FACT-Lym also asks subjects about their concerns about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. Other exploratory endpoints include resolution of B symptoms (fevers over 100.4, drenching night sweats, weight loss of over 10%) and pruritus. We will also record the time it took between enrollment to resolution of these symptoms and the duration of the disease-related symptoms.

7.7 Subject Population for Analysis – Phase II

In order to be included in the tolerability review, a subject must have received the cohort-specific dose of itacitinib and everolimus for at least 75% of the days during the 28-day DLT surveillance period or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size of 3, should withdrawal or dose interruptions/reductions result in a subject being non-evaluable. In order to be included in the efficacy evaluation, a subject must have received at least 21 days of study-specified therapy. Subjects who receive at least one dose of the combined treatment (itacitinib and everolimus) will be assessed for adverse events, survival and exploratory analyses (FACT-lym, resolution of B symptoms or pruritus).

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests organ toxicity.
- The abnormality is of a degree that requires active management.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Dose Limiting Toxicity

See section 3.2 for a description of the Dose Limiting Toxicities (DLT).

8.2 Expected Adverse Events

Refer to the itacitinib Investigator's Brochure and the everolimus package insert for the expected adverse events.

8.3 Recording of Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects using the Common Toxicity Criteria version 5 at each study visit. Participants will be monitored by medical histories, physical examinations, and other studies. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject during the treatment phase of the study (before EOT), the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)

3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution, the end of study visit, or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Related AEs should be followed until resolution, lost to follow up, or judged to be permanent.

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Reporting period

Adverse events will be reported from the time of informed consent until EOT visit. Once a subject enters into the safety follow up period as described in section 6.4.8, subjects will only be followed for unresolved adverse events.

Investigator reporting: notifying the study sponsor

Every SAE, regardless of suspected causality (e.g., relationship to study drug(s) or study procedure or disease progression) must be reported to the sponsor within 24 hours of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the notification (MedWatch or CIOMS form) to the Sponsor.

New information regarding the SAE will be reported as it becomes available and in the same manner as the initial SAE (i.e. MedWatch or CIOMS). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer, up to 6 months from the last treatment.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to his/her IRB/EC of record and other local regulatory groups per the local requirements.

8.5 Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug or process may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug and/or process, the following procedures should be followed to ensure subject safety:

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.6 Protocol Exceptions and Deviations

Exception (Prospective action)

An ***exception*** is defined as a one-time, intentional action or process that departs from the approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcomes may be compromised, or the action compromises the safety and/or welfare of study subjects, advance documented approval from the Regulatory Sponsor and local regulatory review committees, per institutional guidelines, is required. Approval from the Regulatory Sponsor must be received prior to submission to the local regulatory review committees.

Deviation (Retrospective action)

A ***deviation*** is defined as a one-time, unintentional action or process that departs from the approved study protocol, involving one incident and identified retrospectively. If the deviation disrupts study progress, such that the study design or outcomes may be compromised, or the deviation compromises the safety and/or welfare of study subjects, the deviation must be reported to the Regulatory Sponsor within 5 days of PI knowledge and to local regulatory review committees per institutional guidelines.

Report the following information on the Sponsor's exception/deviation form:

- Protocol number
- Subject number
- Description of the exception or deviation
- Rationale
- Impact on subject safety
- Impact on data integrity

Deviations that are assessed by the PI to not disrupt the study progress, such as not affecting the study design or outcome, or compromising the safety and/or welfare of study subjects, should be documented in site records and contain documentation of the PI's assessment.

8.7 Stopping Rules (safety and efficacy)

The safety analysis is based on Bayesian probability calculations and will be performed after the first 6 subjects treated at the RP2D and then after enrollment of 9, 12, and 15 subjects at RP2D dose. The maximum rate of unacceptable toxicity (AEs that would fit the definition of DLT from phase 1 at any point or AEs that do not allow the subject to restart treatment within 28 days) is 30% and a beta prior of (1,5) is assumed (that is 1 unacceptable toxicity in 6 subjects). The study will be terminated if 4 unacceptable toxicities in 6 subjects, 5 in 9, 6 in 12, or 7 in 15 are observed. The posterior probability that the true rate of unacceptable toxicities is above 30% at each stopping would be around 77 to 79% (79%, 78%, 78%, and 77%, respectively).

The efficacy analysis is based on Simon 2 stage optimal design and will be performed after the enrollment of the first 9 evaluable subjects treated at the RP2D. If there are no responders with CR from the first 9 evaluable subjects (at the 8 week or 16 week response assessment, at any itacitinib dose level), the null hypothesis (CR rate of 5% or lower with the new combination) will be considered as supported, and the study will be terminated. The study will be considered successful if the total number of subjects with CR is ≥ 2 in Phase II (at the 8 week or 16 week response assessment).

If there are two (2) study related deaths during the phase I portion of the trial, the study will be terminated.

Any death in the Phase II portion will result in pausing enrollment of the study until investigation is completed. If there are two (2) study related deaths in the Phase II portion of the study will be terminated.

8.8 Monitoring

This study will be monitored according to the Sponsor Data and Safety Monitoring Plan.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), has adequate space to conduct the monitoring visit, and that site staff, including the PI, can meet with the monitor to discuss findings.

8.9 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Notify the Sponsor in real-time if an audit/inspection notification is received.

9 STUDY ADMINISTRATION, DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (EDC) via PennCTMS/VELOS. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Data Collection and Management

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, subject records, and public records/databases at intervals of about 12 weeks.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (e.g., subsequent anticancer treatments and survival), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

9.5 Records Retention

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with applicable regulations (at least 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

10 ETHICAL CONSIDERATIONS

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

The protocol is listed on clinicaltrials.gov.

10.1 Risks

Refer the itacitinib investigator's brochure for the risks associated with itacitinib. Refer to section 5.6.2 and the everolimus package insert for the risks associated with everolimus.

10.2 Benefits

The combination of oral therapies has potential to be active in subjects with relapsed/refractory HL. Also, both agents are oral which makes this therapy convenient for subjects.

10.3 Risk Benefit Assessment

The potential benefits (effective oral therapy for subjects with limited options) outweigh the risks of this combination.

10.4 Informed Consent Process / HIPAA Authorization

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures. Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. A copy of the signed ICF must be provided to the study subject.

10.5 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11 PUBLICATION PLAN

Publication of the results of this trial will be governed by University of Pennsylvania policies. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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13 APPENDIX

13.1 FACT-Lym Questionnaire

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

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

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	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
Ga1	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

13.2 Concomitant Medications/Products not to be taken

Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A4 and or P-gp (Note this is not an exhaustive list):

Excluded
Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit
Strong CYP3A inhibitors:
boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole
Moderate CYP3A inhibitors:
amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil
Strong CYP3A inducers:
avasimibe, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort
Moderate CYP3A inducers:
bosentan, efavirenz, etravirine, modafinil, nafcillin
Cautionary
Weak CYP3A inhibitors:
alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton
Weak CYP3A inducers:
amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib
P-gp Inhibitor:
amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, ticagrelor

Please note:
- strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates (the distinction is not always categorical as interaction can vary according to conditions).

13.3 ECOG Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

**Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982 Available at: http://www.ecog.org/general/perf_stat.html. Accessed April 26, 2018.

13.4 Revised Criteria for Response Assessment of Malignant Lymphoma[19]

The following table provides a summary of response criteria for malignant lymphoma according to Cheson (2014). Please refer to published international guidelines for the most recent and complete details.

Site	PET-Based Response	CT-Based Response
	Complete metabolic response	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS.[a]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
	Partial metabolic response	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	• Score 4 or 5a with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At EOT, these findings suggest residual disease.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consider further evaluation with MRI or biopsy.	Not applicable.
Lymph nodes and extralymphatic sites	• Score 4 or 5a with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At EOT, these findings suggest residual disease.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.

Site	PET-Based Response	CT-Based Response
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
	No metabolic response	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score of 4 or 5a with no significant change in FDG uptake from baseline at interim or EOT.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.
	Progressive metabolic disease	**Progressive disease (requires at least 1 of the following)**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5a with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: New or recurrent FDG-avid foci.	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm. – Increase by ≥ 50% from PPD nadir. – Increase in LDi or SDi from nadir: ▪ 0.5 cm for lesions ≤ 2 cm. ▪ 1.0 cm for lesions > 2 cm. • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of preexisting nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. New or recurrent involvement of the bone marrow

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

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

13.5 New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

13.6 Regimens for *Pneumocystis* Pneumonia Prophylaxis

DRUG	DOSE
Preferred regimen	
Trimethoprim-sulfamethoxazole	1 DS tablet Monday-Wednesday-Friday
Alternative regimens	
Dapsone	100 mg daily
Atovaquone suspension	1500 mg orally once daily given with food
Aerosolized pentamidine	300 mg monthly (via Respigard II nebulizer)