A Multicenter Phase I Study of Ibrutinib in Relapsed and Refractory T-cell Lymphoma

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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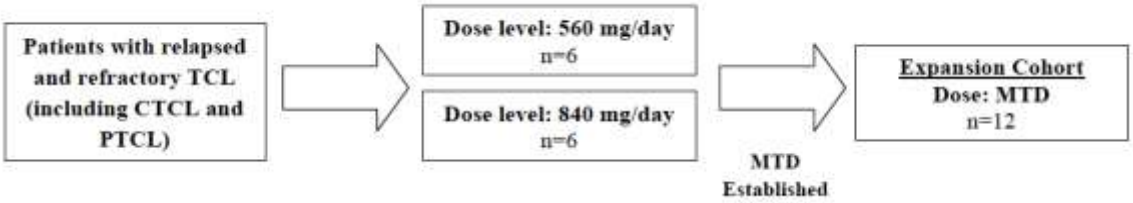
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

In this phase I study, we plan to determine the maximal tolerated dose of ibrutinib in relapsed and refractory T-cell lymphoma (TCL). This will be a modified dose-escalation study to assess the safety of ibrutinib in relapsed/refractory TCL.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objectives of this study are:

- To evaluate the safety and toxicities of ibrutinib in patients with relapsed/refractory T-cell lymphoma (PTCL and CTCL) as defined by CTCAE version 4 and establish the maximum-tolerated dose (MTD) and recommended expansion dose.

The secondary objectives of this study are:

- To preliminarily explore the therapeutic efficacy of Ibrutinib in patients with PTCL and CTCL. We will assess outcomes of overall response rate (ORR), complete response rate (CR), partial response rate (PR), the duration of response (DOR), progression free survival (PFS), and event free survival (EFS).
- To perform correlative studies to gain insight into the mechanism of action of ibrutinib in T-cell lymphoma and identify potential subgroups of patients who respond to the agent.

3.0 BACKGROUND AND RATIONALE

3.1 PTCL

Peripheral T-cell lymphoma (PTCL) represents a heterogenous group of diseases. Systemic forms of PTCL are associated with poor outcomes and limited survival.[1] Cutaneous T-cell lymphomas (CTCL), a subtype of PTCL, generally has a more favorable prognosis, however, advanced stage CTCL does require systemic therapy and is associated with reduced survival as well.[2] In recent years, new agents have been studied to improve outcomes for patients with relapsed and refractory PTCL, such as pralatrexate, romidepsin, and brentuximab vedotin.[3-5] Nevertheless, many patients with relapsed, refractory PTCL fail to respond to these agents and continue to have poor outcomes.[6] A recent study from the British Columbia Cancer Agency reported a median overall survival of 5.5 months for patients with relapsed, refractory PTCL treated in the modern era, indicating the need for novel therapeutic strategies in this field.[6]

3.2 Ibrutinib

Ibrutinib, an oral, small-molecule, irreversible Bruton's tyrosine kinase (BTK) inhibitor, has demonstrated promising clinical activity in phase I/II trials of B-cell malignancies. BTK is an important tyrosine kinase in the B-cell receptor (BCR) signaling pathway, and chronic activation of this pathway is implicated in the pathogenesis of B-cell malignancies.[7, 8] A recent phase I study of ibrutinib in various B-cell malignancies showed that ibrutinib was well-tolerated with an excellent safety profile and was associated with an objective response rate of 60%.[9] Across five dose levels (1.25, 2.5, 5.0, 8.3, and 12.5 mg/kg/day), there were only 2 DLTs that occurred (of 56 total patients), one grade 3 allergic hypersensitivity in a patient with a history of drug hypersensitivity and one dose interruption for more than 7 days due to transient grade 2 neutropenia. There was no consistent relationship between dose level and adverse events. An MTD was not reached. Therefore, for an average 70kg person, doses ranging from 87.5 mg/day to 875 mg/day were found to be safe in the phase I study. For further study in B-cell non-Hodgkin lymphoma, an optimal biologic dose of 560 mg/daily was established and associated with full BTK receptor occupancy. Recently published phase II studies of ibrutinib also demonstrated that the drug is well-tolerated at a dose of 560mg/daily in mantle cell lymphoma and 420 mg/daily in chronic lymphocytic leukemia.[10, 11]

3.2.1 Monotherapy Studies

The integrated safety profile of ibrutinib administered as monotherapy to 506 subjects across several clinical studies (PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1106-CA, PCI32765MCL2001, PCYC-1111-CA, PCYC-1117-CA, and PCI-32765-JPN-101) has been evaluated. The most common treatment-emergent adverse events as of 06 April 2013 were diarrhea (42.1%), fatigue (33.8%), nausea (26.1%), cough (20.2%), and peripheral edema (18.6%). Grade 3 or 4 adverse events were experienced by 60.7% of subjects, the most common (> 2%) of which were hematologic in nature: neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Pneumonia (7.7%) was the most frequent nonhematologic Grade 3/4 adverse event. Serious adverse events were experienced by 46.4% of treated subjects.

The only serious events occurring in more than 2% of subjects (excluding disease progression) were pneumonia (7.9%), atrial fibrillation (3.2%), and febrile neutropenia (2.8%).

As of 6 April 2013, 62/506 subjects discontinued treatment due to an adverse event, across the monotherapy ibrutinib studies (excluding Study PCYC-1103-CA); the most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), cardiac arrest (3 subjects) and Richter's Syndrome (3 subjects).

3.2.2 Treatment related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood.[12]

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (33%)

with relapsed/refractory MCL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL patients.

A substantial increase in the number of circulating lymphocytes (e.g., > 400,000/mcL) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (>400,000/mcL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and the Principal Investigator should be contacted.

3.2.3 Hemorrhagic Adverse Events

There are reports of hemorrhagic events in subjects treated with ibrutinib in both monotherapy and combination clinical studies. The majority of these hemorrhagic adverse events were of Grade 1 or 2 in severity, including minor hemorrhagic events like contusion, epistaxis and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Hemorrhagic events of Grade 3 or higher, including central nervous system hemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies. It is not clear whether or not these events are attributable to ibrutinib; however, it is possible that treatment with the study drug could increase the risk of bruising or bleeding.

Subjects were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Therefore, ibrutinib should not be not administered concomitantly with warfarin or other vitamin K antagonists. Ibrutinib should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided. Patients with congenital bleeding diathesis have not been studied.

Subjects in the current study will be monitored closely for hemorrhagic adverse events. Ibrutinib should be held at least 3 to7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding (please refer to Section 9.2.3 for further details).

3.2.4 Rash

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

3.2.5 Infection

In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥ Grade 3; 25.2%) and CLL/SLL (≥ Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death. Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.

3.2.6 Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Subjects with a history of cardiac arrhythmias should be monitored closely.

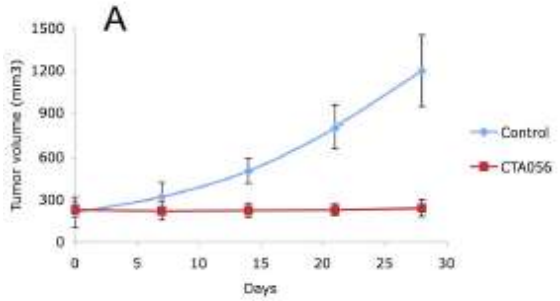
3.3 Rationale for evaluating ibrutinib in peripheral T-cell lymphoma (PTCL):

In preclinical studies ibrutinib has been shown to not only inhibit BTK, but also inhibits a number of TEC family kinases *in vitro*, including interleukin-2-inducible T-cell kinase (ITK).[8, 13, 14] Interleukin-2-inducible T-cell kinase (ITK) is an important kinase in the T-cell receptor (TCR) signaling pathway that regulates T-cell proliferation, differentiation, and activation through regulation of phospholipase C-gamma (PLC-γ) activation leading to intracellular calcium flux, ERK activation, cytokine release, and transcriptional activation in T-cells. Another TEC family kinase, resting lymphocyte kinase (RLK or TXK), also contributes to TCR signaling in conjunction with ITK. ITK plays a critical role in the activation of the CD4+ effector T-cell subset, type 2 helper T-cells (Th2).[15, 16] ITK is expressed in normal and malignant T-cells.[17] ITK mutations in humans have been associated with EBV-associated lymphoproliferative disorders and were first described in two siblings from a consanguineous Turkish family who died of fatal Epstein-Barr Virus infection, resulting from severe immune dysregulation including absent or reduced natural-killer T-cells and altered T-cell differentiation.[18, 19] ITK knock-out mice have altered immunity, and fail to generate Th2 response to infections and have defects in T-cell receptor signaling.[16, 20-22] Increased ITK expression has been reported in adult T-cell leukemia/lymphoma cell lines (Jurkat and Molt4) and in skin lesions of patients with CTCL,[23, 24] however, the role of ITK in promoting T-cell malignancy is not known.

A landmark study by Dubovsky *et al* showed that ibrutinib is an irreversible ITK inhibitor and reduces downstream activation of TCR pathway in Jurkat cell lines.[14] Furthermore, functional ITK inhibition was shown with decreased levels of phosphorylated PLC-γ using phosphoflow analysis of CD4 T-cells from patients with CLL treated with ibrutinib.[14] An alternate selective inhibitor of ITK, CTA056, was found to inhibit phosphorylation of ITK and decrease levels of

its downstream effectors in the T-cell receptor pathway, such as phosphorylated PLC-γ, Erk, and Akt.[23] CTA056 inhibited the growth of Jurkat and Molt4 cell lines. In mice injected subcutaneously with ten million MOLT-4 cells (human acute lymphoblastic leukemia cell line), tumors developed and mice were treated with vehicle (control) or CTA056 (ITK inhibitor) – see Figure 1. Tumor stability was noted in mice treated with ITK-inhibitor versus progressive tumor growth in untreated mice.

Figure 1. Inhibition of MOLT-4 xenograft tumor growth by ITK inhibitor, CTA056 (reproduced from Guo *et al*.)[23]



This preclinical work suggests that ITK may play a key role in promoting malignant T-cell proliferation and survival.

In addition, ITK promotes Th2 differentiation and Th2-cytokine production. Inhibition of ITK has been shown to result in a Th1 versus Th2 effector T-cell bias.[14] ITK-deficient mice mounted a protective Th1 response to *Leishmania major* infection and failed to develop a robust Th2 immune response to parasitic infection with *Nippostrongylus brasiliensis*.[20] Dubovsky *et al* also demonstrated in a listeriosis/CLL mouse model that ibrutinib treatment allowed mice to survive a potentially lethal *Listeria monocytogenes* infection due to selective expansion of cytotoxic Th1 based immunity.[25] A bias toward Th2 versus Th1 effector cells has been described in malignancy, and is hypothesized to facilitate evasion of host immune attack with a decrease in cytotoxic Th1 T-cells. In PTCL, a Th2 cell–rich environment has been noted in cutaneous T-cell lymphoma (CTCL) and HTLV-1-infected T-cells.[26-30] In leukemic CTCL (Sezary syndrome), both benign and malignant T-cells have been shown to have a strong Th2 bias, leading to suppression of Th1 responses (reduced production of IFN-γ).[29] In fact, effective therapies in CTCL have been associated with restoration of Th1/Th2 imbalance, for example, extracorporeal photochemotherapy, IFN-α2b, UVB phototherapy, and low-dose alemtuzumab, resulted in decreased Th2 associated cytokines (IL-4, IL-5) and increased production of Th-1 cytokine pattern (IFN-γ, IL-2).[28, 29]

We hypothesize that ibrutinib may provide therapeutic benefit in PTCL/CTCL by inhibiting ITK which may 1) downregulate pro-survival signaling through the TCR pathway and 2) augment immune surveillance of malignant T-cells with increased cytotoxic Th1 based immunity.

3.4 Rationale for Correlative Studies

We plan to perform exploratory biomarker analysis to gain insight into ibrutinib's mechanism of action in PTCL and to explore biomarkers that may predict treatment response. These are described below.

1) ITK-Occupancy in peripheral blood mononuclear cells

The proposed mechanism of action of ibrutinib in PTCL is mediated through ITK inhibition, therefore, we aim to assess ITK occupancy to establish that ibrutinib is binding the therapeutic target, ITK, and to correlate ITK occupancy with response. We plan to measure ITK occupancy in peripheral blood mononuclear cells (PBMC) using the biotinylated affinity probe assay.[8, 9] The ITK-occupancy biotinylated affinity probe assay measures the relative amount of ITK that has not been bound by the ITK-inhibitor, ibrutinib.

It is not clear what threshold of ITK occupancy is required for a therapeutic effect in T-cell lymphomas. In CLL patients treated with ibrutinib who had PBMC tested for ITK occupancy using the ITK biotinylated affinity probe assay, it was found that at a dose level of 420 mg/daily, ITK occupancy ranged from 40-80%.[25] At higher doses of 840 mg/daily, occupancy levels were not clearly higher when compared to 420 mg/daily and the maximum ITK occupancy seen was also 70-80% (personal communication Dr. Betty Chang and Joseph J Buggy, Pharmacyclics). Regardless of dose, it does not appear that maximal ITK occupancy will exceed 80%, likely due to multimerization of ITK molecules in the cytoplasm which serves as an ITK regulatory mechanism. Furthermore, preliminarily there does not appear to be a dose-dependent increase in ITK-occupancy at higher levels of ibrutinib. In this trial, we will test ITK-occupancy at the two dose levels, 560 and 840 mg/day, and will correlate degree of ITK-occupancy with response.

The methods of the ITK occupancy assay are analogous to the BTK occupancy assay that has been previously published.[8, 9] In brief, blood samples will be collected at the same time points used to assess BTK occupancy, on day 1 (predose), day 8 (predose), and day 28 (predose), in order to assess occupancy levels throughout the 28-day cycle.

In the Pharmacyclics central laboratory, the ELISA biotinylated ITK probe assay, based upon an electrochemiluminescent assay, will be used to determine the relative amount of ITK that has not been bound by the ibrutinib. Ibrutinib binds to the active site of ITK and forms a disulfide bond with a cysteine residue (ITK-Cys442). PCI-41025 is a probe that consists of ibrutinib linked to biotin via a long chain linker. The collected PBMC and protein lysates are labeled with a biotinylated derivative of drug, PCI-41025. Labeling of samples with the probe allow for the detection of ITK not occupied by drug. The probe conjugated with ITK (and un-conjugated probe) is captured by the Streptavidin (SA) plate that is subsequently incubated with mouse anti-ITK (BD#550503) and SULFO-TAG conjugated anti-mouse antibody (MSD, cat#R32AC-5). The SULFO-TAG labels emit light upon electrochemical stimulation initiated at the electrodes in each well and signal is measured. A larger the signal correlates to more unoccupied ITK sites of a sample while a lower signal correlates to more ibrutinib occupied ITK sites.

The baseline for ITK occupancy will be set at the pre-dose Cycle1 Day 1 sample and the percent of ITK occupancy at the prescribed time points will be calculated by this baseline value. This percentage will be used as the pharmacodynamic output and compared between different dose cohorts of patients. Thus the relationship between the ibrutinib dose cohort and ITK occupancy will be defined.

The development, methods, and performance of this assay are described in detail in the attached "Pharmacyclics ITK and BLK Occupancy Assay" development report in Appendix 1.

We plan to collect a number of biospecimens, as detailed in Appendix 7, to perform correlative studies to gain insight into the mechanism of action of ibrutinib in T-cell lymphoma and identify potential subgroups of patients who respond to the agent. Potential correlative studies that we plan to perform in the future are outlined below. However, details regarding correlative studies will be determined in the future depending on biospecimen availability and funding source.

2) Evaluate the in vivo effect of ibrutinib on helper T-cell polarization (Th1 vs. Th2) .

As described above, patients with PTCL/CTCL have been found to have increased levels of Th2 cytokines.[26-30] Ibrutinib, via ITK-inhibition, has been shown to be associated with potentiation of Th1-based immunity and a decrease in Th2 immune responses.[25] We plan to test for changes in helper T-cell polarization from Th2 to Th1-dominant responses. Examples of potential correlative studies we may perform to explore this hypothesis include measurement of1) serum cytokine levels, 2) gene-expression profiling using Nano-String technology, and 3) GATA3 and TBX21 protein expression by immunohistochemistry (IHC).

<u>Serum cytokine levels</u>

This shift from Th2 toward Th1 immunity may be detected through measurement of intracellular levels of Th1 cytokines and Th2 cytokines. One approach would be to perform multiplex cytokine analysis with measurement of serum levels of Th1 cytokine markers (IFN-γ, IL-2, TNF-β) and Th2 cytokine markers (IL-4, IL-5, IL-6, IL-10, IL-13) pre and post treatment.

<u>Gene Expression Profiling using Nanostring technology</u>

To assess changes in Th1 and Th2 polarization at the tumoral level, we plan to use the novel Nanostring technology to measure gene expression level based on RNA from formalin-fixed paraffin-embedded tissue (FFPET). For such an experiment, we would compare results FFPET pre-treatment (baseline) and post-treatment (day 8).

<u>Protein expression of GATA3 and TBX21 by IHC</u>

Recent work by Iqbal *et al* identified two prognostically-relevant and mutually exclusive molecular subgroups defined by increased expression of GATA-3 or TBX21 in patients with peripheral T-cell lymphoma, not otherwise specified. Elevated GATA-3 expression was associated with inferior overall survival. The GATA-3 protein is an important Th2 specific

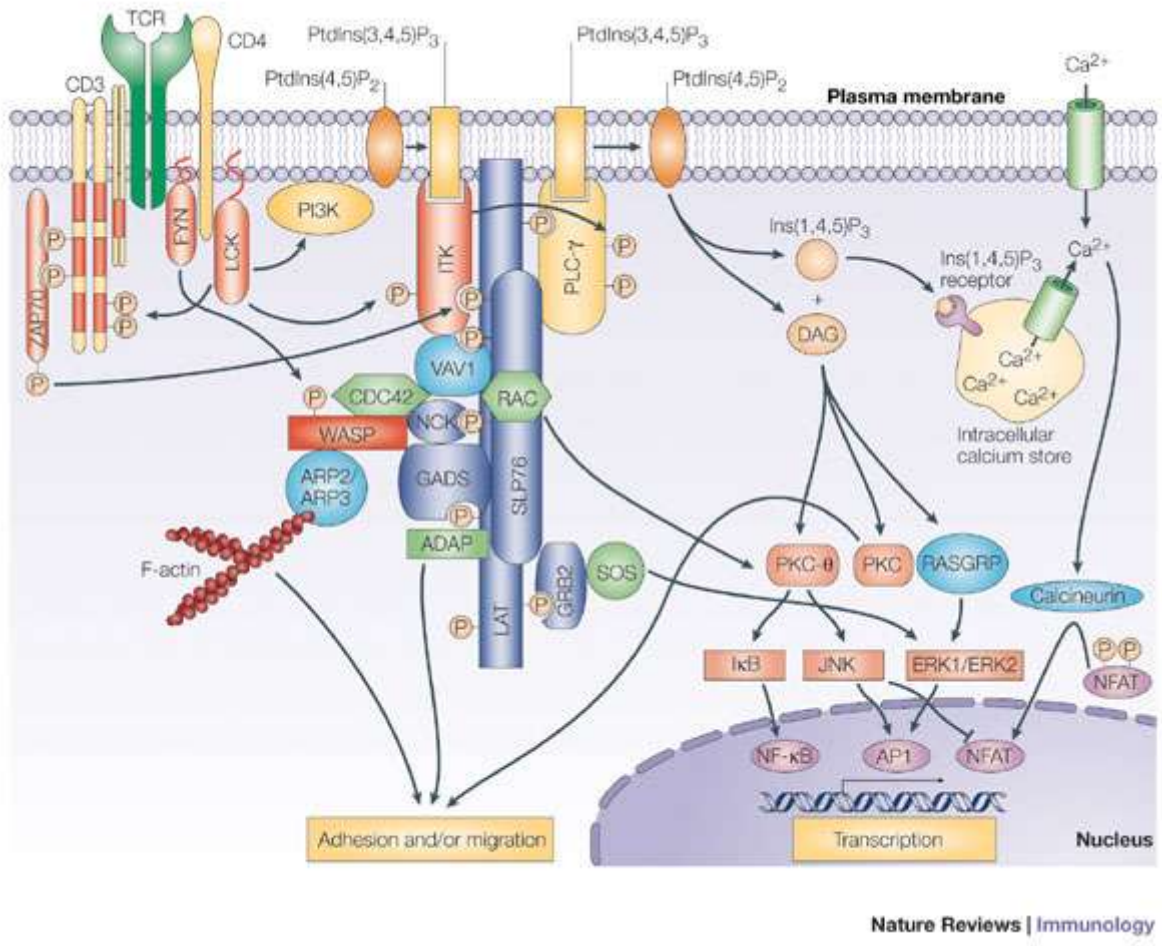
transcription factor associated with the secretion of Th2 associated cytokines including IL-4, IL-5, and IL-13 while the TBX21 (T-bet) protein is a Th1 cell-specific transcription factor that controls production of IFNγ. In this study, expression of GATA-3 and TBX21 was assessed using RNA-based gene expression profiling with microarray technology (Affymetrix Inc, CA) and increased expression levels were confirmed using immunohistochemical staining on de-paraffinized tissues sections with GATA3 (mouse monoclonal antibody, clone HG3-35, 1:25, Santa Cruz Biotechnology, Santa Cruz, CA) or TBX21 (mouse monoclonal antibody, clone

4B10, 1:100, BD Biosciences, San Jose, CA). IHC successfully distinguished the TBX21 and GATA3 subgroups defined by increased expression on GEP. With the TBX21 immunostain, the TBX21 subgroup showed positivity ranging from 40- 80% cells whereas the GATA3 subgroup was less than 10%. Similarly, with the GATA3 immunostain, the GATA3 subgroup showed positivity ranging from 50-80% cells whereas the TBX21 subgroup was less than 1%.

In the current study, we plan to perform immunohistochemical staining with GATA3 and TBX21 antibodies as previously described on tissue sections pre-treatment (baseline) and post-treatment (day 8). In this preliminary analysis, we will explore whether patients with increased GATA-3 expression will demonstrate response to ibrutinib given that these tumors may be supported by a Th2-skewed immune microenvironment that may be reversed by ibrutinib therapy.

3) Evaluate the effect of ibrutinib therapy on ITK signaling pathway.

We plan to use phosphoflow analysis to assess the impact of ITK inhibition on downstream effects in TCR pathway. ITK and other Tec family kinases (RLK and TEC) are key components of T-cell receptor signaling. The figure below (reproduced from Schwartzberg *et al*[21]) depicts the role of ITK in the TCR pathway. ITK leads to phosphorylation of PLC-γ that leads to the breakdown of phosphatidylinositol-4,5-bisphosphate into inositol trisphosphate (IP_3) that stimulates Ca^{2+} mobilization and diacylglycerol (DAG) activation. DAG activates protein kinase C (PKC) and leads to downstream activation of ERK1/ERK2.



To assess the effect of ibrutinib on the TCR signaling pathway, we will plan to assess phosphorylation of PLC-γ using phosphoflow analysis as previously published by Dubovsky *et al*.[25] PLCγ1 is directly phosphorylated at Tyr783 by ITK. We will plan to perform pPLCγ1-Tyr783 phosphoflow analysis to assess the percentage of activated T-cells with phosphorylated-PLCγ1 before and after treatment with ibrutinib. We hypothesize that treatment with ibrutinib will result in decreased levels of phosphorylated-PLCγ1 as has been previously demonstrated in patients with CLL treated with ibrutinib. PBMCs will be collected day 1 cycle 1 and day 8 cycle 1 for these studies.

4) T-cell subsets

We will plan to assess T-cell (including naive and memory T-cells), B-cells, and NK T-cell subsets using a flow cytometry assay performed on whole peripheral blood samples collected pre-treatment and post-treatment (day 1 cycle 1, day 8 cycle 1, and day 1 cycle 2). In ITK-deficient mice and humans with ITK-mutations, there has been evidence of absent or decreased NK T-cells, and we will aim to assess whether there are changes in the proportion of NK T-cells after treatment with ibrutinib.[19, 32] It will also be interesting to assess whether ibrutinib changes the proportion of naive versus memory T-cell populations.

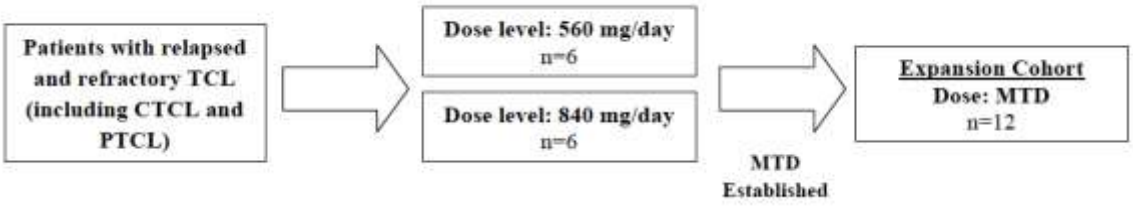
5) We will plan to bank any tissue specimens collected at MSK from this study for future research to identify biomarkers for response to ibrutinib. Any optional baseline tissue specimens collected at Ohio State University (OSU) should be sent to MSK at the end of the study. Mutations associated with TCL pathogenesis are increasingly being elucidated. In the future, we may examine the impact of baseline genetic alterations on treatment response using targeted next-generation DNA sequencing.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

4.1.1 Overall Study Design

This will be a multi-center phase I trial of ibrutinib in patients with relapsed/refractory T-cell lymphomas. The study schema is shown below.



In this study, we will enroll patients with any pathologically confirmed relapsed or refractory mature T-cell lymphoma PTCL and CTCL. The two most common forms of CTCL are mycosis fungoides (MF) and Sezary syndrome (SS).

4.1.2 Phase I Dose-Escalation

This will be a standard dose-escalation study to determine the MTD of ibrutinib in relapsed/refractory PTCL or CTCL. At each dose level (shown in the table below), 6 patients with TCL (PTCL or CTCL) will be enrolled. The first 6 patients will be enrolled at dose level 1. Dose escalation to the next dose level will proceed after DLT assessment of all 6 patients at the end of cycle 1 (28-days).

We plan to test the following doses:

Dose Level*	Ibrutinib
-1	420 mg/day
1	560 mg/day
2	840 mg/day

*Additional dose levels may be tested based upon toxicity and response assessment at dose levels 1 and 2 at the discretion of the MSK principal investigator after discussion with Pharmacyclics. Addition of new dose levels would require an amendment.

Patients will receive ibrutinib capsules orally once daily on a 28-day cycle administered continuously until disease progression or intolerance.

In the absence of DLT, each subject will be treated for a minimum of 28 days, and may continue to receive additional treatment until disease progression has been documented, intolerance, or other treatment discontinuation criteria have been met.

No intrasubject dose escalation will be allowed.

Safety and tolerability will be assessed by the incidence and severity of adverse events as determined by the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.03).

4.1.3 Definition of Dose Limiting Toxicity

DLT will be defined during cycle 1. A DLT will be defined as any of the following adverse events (AE) occurring up to 7 days following completion of study drug dosing during cycle 1 and at least possibly related to the study drug:

- Grade 4 toxicity: hematologic
- Grade 4 toxicity or persistent Grade 3 toxicity that fails to improve with conventional therapies: gastrointestinal
- Grade ≥3 toxicity: any other drug-related non-hematologic toxicity
- Dose delay of > 10 days related to toxicity

We will plan to monitor for DLT during cycle 1.

4.1.4 Definition of MTD and Recommended Expansion Dose

MTD

The MTD will be defined as the dose level below the dose at which ≥33% (i.e. 2/6 patients) experience a DLT, or, in absence of a DLT-defined dose level, the MTD will be defined as the highest dose tolerated.

Recommended Expansion Dose

The recommended expansion dose is the dose level below the dose at which ≥33% (i.e. 2/6 patients) experience a DLT, or, in absence of a DLT-defined dose level, the dose level with evidence of the highest level of preliminary efficacy, which is defined as the overall response rate within the first two cycles.

4.1.5 Expansion Cohort

After the recommended expansion dose is established, an expansion cohort of 12 additional patients will be treated at the recommended expansion dose to further characterize the safety at that dose and to further assess preliminary efficacy. Given the differences in clinical presentation and disease biology between CTCL and PTCL, we aim to treat an equal

number of patients with CTCL and PTCL at the recommended expansion dose in order to assess for unique toxicities or response profiles. For example, if 4 patients with CTCL and 2 patients with PTCL were treated at the recommended expansion dose in the dose-escalation phase, then we would treat 5 patients with CTCL and 7 patients with PTCL in the expansion cohort (so a total of 9 patients with each disease subtype will be treated at the recommended expansion dose).

Based on early signals of efficacy, additional patients may be added to the expansion cohort through an amendment.

In absence of DLT, each subject will be treated for a minimum of 28 days and may continue to receive additional treatment until disease progression has been documented, intolerance, or other treatment discontinuation criteria have been met.

Patients will undergo restaging evaluation with after cycles 2, 4, 6, 9, 12, and thereafter approximately every 6 months at the physician's discretion. The antitumor activity of the study treatment will be assessed according to standard response criteria as appropriate for each individual subject's tumor type (described in Section 12.0).

4.2 Intervention

All patients will be treated with ibrutinib orally on days 1-28 of a 28-day cycle. The dose will be determined by the cohort they are registered into. Once the MTD is established, this dose level will be used for expansion cohort and will be administered once daily continuously until PD or intolerance.

Patients receiving ibrutinib will be monitored per study guidelines for one year after initiating ibrutinib treatment. After 1 year, responding patients can continue to receive ibrutinib, however, will be followed at the discretion of the treating physician. For patients who stop taking the study drug for whatever reason, but do not have evidence of disease progression, we will continue to monitor these patients for disease progression or death. If not otherwise seen at regular clinic visits, a member of the medical team will contact these patients by telephone every 6 months to determine and track disease status.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Ibrutinib, the investigational treatment in this protocol, is an orally-administered, small-molecule inhibitor of BTK. Further detail regarding ibrutinib may be found in the current Investigator's Brochure (Appendix 2).

Physical Description of Study Drug(s)

Ibrutinib capsules are provided as white opaque capsules containing 140mg of ibrutinib as the active ingredient. Ibrutinib will be manufactured and provided by Pharmacyclics.

Packaging

Ibrutinib capsules will be packaged in bulkin opaque high-density polyethylene (HDPE) child-resistant plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies.

Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. The investigational products will be labeled as open-label material. Each bottle of ibrutinib will contain a study specific label with a unique identification number.

Preparation, Handling, and Storage

Study drug will be stored at the study site in a secure area with restricted access until dispensed to the study subjects. Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage condition. Formal ICH stability studies are ongoing to determine the shelf-life of the product.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and faxed to Pharmacyclics. Refer to the Investigator's Brochure for additional information regarding storage and handling of ibrutinib.

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F). Retain in the original package.

Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the instructions from Pharmacyclics. Study site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by Pharmacyclics, upon request. The return of unused study drug to Pharmacyclics, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the MSK principal investigator (PI), site PI, or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The MSK PI or site Plagrees neither todispense the study drug from, nor store it at, any site other than the study sites agreed upon by the MSK principal investigator and Pharmacyclics.

Subjects will be given diary cards to complete for the ibrutinib dosing at home. The subjects must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Patient with relapsed, refractory T-cell lymphoma will be enrolled in this study.

6.1 Subject Inclusion Criteria

- Pathology confirmed relapsed or refractory T-cell lymphoma (PTCL and stage >IB CTCL) at treating institution.
- Relapse or progression after at least 1 systemic therapy.
- Age ≥18 years at the time of signing the informed consent form.
- Able to adhere to the study visit schedule and other protocol requirements.
- Previous systemic anti-cancer therapy must have been discontinued at least 3 weeks prior to treatment in this study. If there is progression of disease on that therapy and all adverse effects have resolved to Grade 1 or baseline, in which case 2 weeks is acceptable.
- Previous radiation, hormonal therapy, and surgery must have been discontinued at least 2 weeks prior to treatment in this study and adverse effects must have resolved. Lymph node or other diagnostic biopsy within 2 weeks is not considered exclusionary.
- Systemic corticosteroids are permissible in the following circumstances:
    - Short course systemic corticosteroids for disease control, improvement of performance status or non-cancer indication (≤ 7 days) must have been discontinued at least 7 days prior to study treatment.
    - Ongoing administration of a stable dose of corticosteroid therapy (previously received for ≥ 30 days) is permissible provided there is evidence of measurable disease and there will be no increase in steroid dose during the clinical trial.
- ECOG performance status of ≤ 2 at study entry.
- Patients who have undergone autologous stem cell transplant > 6 months prior are eligible.
- Patients who have undergone allogeneic stem cell transplant > 12 months, without active graft-versus-host-disease, and not on immunosuppression for prevention of graft-versus-host disease are eligible
- Laboratory test results within these range:
    - Adequate hematologic function with screening laboratory assessment defined as:
        - Absolute neutrophil count >1,000 cells/mm^3 (1.0 x 10^9/L).
        - Platelet count >75,000 cells/mm^3 (75 x 10^9/L), if thrombocytopenia is due to bone marrow involvement platelet count must be ≥ 50,000 cells/mm^3.

- Hemoglobin >8.0 g/dL.

- Adequate hepatic and renal function with screening laboratory assessment defined as:
  - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN).
  - Creatinine <2.0 x ULN or Estimated Glomerular Filtration Rate GFR [Cockcroft-Gault] > 30 mL/min.
  - Bilirubin <1.5 x ULN [unless bilirubin rise is due to Gilbert's syndrome (as defined by >80% unconjugated hyperbilirubinemia) or of non-hepatic origin].

- Females of childbearing potential (FCBP)[†] must have a negative serum pregnancy test and agree to use appropriate methods of birth control.

6.2 Subject Exclusion Criteria

- Patients who have a standard curative option for their lymphoid malignancy at current state of disease are excluded. For eligibility on this trial, allogeneic stem cell transplantation is not considered a standard curative option.
- Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc.) within 28 days of the first dose of study drug.
- Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug.
- Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia.
- Treatment with warfarin or other Vitamin K antagonists (eg, phenprocoumon).
- Any life-threatening illness, medical condition, or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk.
- Unwilling or unable to participate in all required study evaluations and procedures.
- Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF).
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
- Unable to swallow capsules, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- Pregnant females. (Lactating females must agree not to breast feed while taking ibrutinib
- Prior use of ibrutinib.

- Concurrent use of other anti-cancer agents or treatments.
- Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) defined by PCR.
- Active concurrent malignancy requiring active therapy.
- Known central nervous system or meningeal involvement (in the absence of symptoms investigation into central nervous system involvement is not required).
- Patients who require treatment with a strong cytochrome P450 (CYP) 3A inhibitor.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Furthermore, eligible patients from the lymphoma service will be identified by individual consenting physicians at the time of medical disciplinary rounds or in clinic at Memorial Sloan Kettering Cancer Center. Similar processes will be used at Ohio State University.

8.0 PRETREATMENT EVALUATION

Prior to initiating treatment:

- Prior biopsy with pathologic confirmation of relapsed / refractory T-cell lymphoma at treating institution. Pathologic analysis will include standard PTCL/CTCL lymphoma immunohistochemistry panel.
- For CTCL patients or PTCL patients with cutaneous involvement, archival tissue (tissue block or 10-20 unstained slides) is acceptable if it has been obtained at least 1 week after completion of the last treatment for relapsed disease. If archival tissue is not available, then repeat pathologic specimen will be required (skin biopsy or peripheral blood sample for Sezary cells).
- For PTCL patients without cutaneous disease, archival tissue (tissue block or 10-20 unstained slides) from biopsy of relapsed PTCL will be requested. If archival tissue is not available, PTCL patients will be asked to provide informed consent for an optional repeat biopsy (ex. lymph node biopsy or bone marrow biopsy).

Within 2 weeks prior to initiating treatment:

- History and physical exam
- ECOG performance Status
- Presence of B-symptoms
- CBC
- Electrolytes (Na, K, Cl, CO2), BUN, Cr, bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase, uric acid, and LDH

Within 4 weeks prior to initiating treatment (for bullets 1-3 must have completed prior therapy before disease assessment):

- Imaging study: 18F-fluorodeoxyglucose-PET/CT scan (CT chest, abdomen, and pelvis can be performed instead of PET/CT in CTCL patients per investigator discretion. If not using PET/CT, a CT neck is required if there is clinical evidence of disease involvement in the neck).
- mSWAT for patient with CTCL
- Sezary panel in patients with Sezary syndrome only
    - Peripheral blood flow cytometry for CD2, CD3, CD4, CD8, CD26, and CD7.
- Electrocardiogram (ECG)
- Hepatitis B surface antigen and hepatitis B core antibody
- Hepatitis C antibody
- Serum β-HCG (premenopausal females only) to assess for pregnancy

Within 6 months prior to initiating treatment

- HIV I and II antibody testing

9.0 TREATMENT/INTERVENTION PLAN

9.1 Ibrutinib administration

Ibrutinib will be administered once daily continuously until disease progression (confirmed by two assessments for CTCL patients only) or intolerance. The dose levels for the Phase 1 portion of the study are specified in Section 4. Either 560 mg (4 X 140 mg capsules) or 840 mg (6 X 140 mg capsules) doses will be administered.

Ibrutinib should be administered at about the same time each day. Ibrutinib is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water. The patient should avoid taking ibrutinib with grapefruit or seville orange juice. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. If the patient misses a dose, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

The missed dose will be recorded via the patient in the diary card. At any given visit, enough ibrutinib capsules for 1 cycle should be dispensed. Unused ibrutinib capsules dispensed during previous visits must be returned and drug accountability recorded. Returned capsules must not be redispensed to any subject. Investigators are prohibited from supplying ibrutinib capsules to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators. The investigator must ensure that subjects receive ibrutinib capsules only from personnel who fully understand the procedures for administering the drug.

Treatment Compliance:
Ibrutinib is given as a fixed daily dose. Study personnel will maintain a log of all study drug supplied to the patient. Drug supplies for each subject will be inventoried and accounted for.

Subjects will be given diary cards to complete for the ibrutinib (continuous) dosing at home. Subjects must bring the diary cards to the site on every visit so study site personnel can check compliance.

The study drug is to be prescribed only by the principal investigator or a qualified physician listed as a subinvestigator on required forms (e.g., Delegation of Authority and Training Log). Records should be kept on the study drug accountability form provided by Pharmacyclics or its designee. Study drugs administration must be recorded in the subject's permanent record. Upon termination of the study, or at the request of Pharmacyclics or its designee, the pharmacist must return drug to Pharmacyclics or its designee, after all drug supplies have been accounted for, unless it is destroyed at the site as agreed upon by both Pharmacyclics and PI.

9.2 Concomitant Medications

9.2.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per institutional guidelines.

9.2.2 Prohibited Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, , experimental therapy, or radiotherapy are prohibited during the Treatment Phase. Routine infusion premedication with corticosteroid doses of > 100 mg IV prednisolone (or equivalent) is not permitted. Red blood cell growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and sargramostim are also prohibited.

9.2.3 Drug-drug Interactions

Patients will be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with their treating physician. All medications taken within 30 days of screening and medications and supportive therapies that are administered during the study must be recorded in the patient's clinical research database (CRDB) and in the source documents. Supportive therapy, that is ongoing at baseline, will be permitted during the treatment phase of the study. If other therapy for the disease is required, continuation of the study treatment should be discussed with the MSK PI. Concomitant medications for other medical conditions are permitted as clinically indicated subject to specific protocol requirements outlined below.

<u>Guideline for Use of CYP Inhibiting/Inducing Drugs</u>

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-}last}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazodone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville

oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 5).

Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors or inducers is provided in Appendix 5; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Concomitant Use of QT Prolonging Agents

Any medications known to cause QT prolongation may be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function.

Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events.

Subjects requiring the initiation of anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib held, the Principal Investigator should be contacted, and ibrutinib should not be restarted until the subject is clinically stable and the reinitiation of ibrutinib is approved by the Principal Investigator. Subjects should be observed closely for signs and symptoms of bleeding.

Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery (including excisional lymph node biopsies). The following guidance should be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

Minor Surgical Procedures
For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

Major Surgical Procedures
For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is

reasonably healed without serosanguineous drainage or the need for drainage tubes.

Other Malignancies
All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Reproductive Toxicity

Reproductive toxicity studies have not been done with PCI-32765. Therefore, women of child-bearing potential who are sexually active must use highly effective contraception during the study and for 30 days after the last dose of PCI-32765. Men who are sexually active, must use highly effective contraception during the study and for 90 days (3 months) after the last dose of PCI-32765. Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue PCI-32765 immediately. Pregnancy in a female subject or a male subject's partner must be reported in the same manner as a SAE.

9.3 Dose Continuation, Modification and Interruption (Cycle 2 and beyond)

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity. The sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy. There will be no dose reductions in cycle 1. Inability to meet treatment criteria will result in holding the dose.

9.3.1 Dose Delay

Treatment with Ibrutinib should be held for any unmanageable, potentially study drug related toxicity, including: non-hematologic toxicity of grade ≥3, hematologic grade 4 toxicity, or grade 3 neutropenia with infection or fever. Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days.

9.3.2 Dose Modification

The actions in **Table 1** should be taken for the following toxicities:

- Grade 4 ANC (< 500/µL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines and use must be recorded in CRF.)
- Grade 3 or 4 platelets (< 50,000/µL); or, in subjects with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of significant bleeding
- Grade 4 platelets (< 25,000/µL); or, in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/µL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy, or any other Grade 4 toxicity and any unmanageable Grade 3 toxicity.
- Any other grade 4 toxicities as defined by the latest version of the CTCAE or any unmanageable nonhematologic grade 3 toxicities.

Table 1. Drug Discontinuation Actions for Subjects on Ibrutinib

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg less daily)*
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg less daily)*
4th	Discontinue ibrutinib

*** Reference Table 2 for details on dose de-escalation of various dose levels.**

Table 2. Intrasubject Dose De-escalation

Assigned Daily Dose	560 mg (4 X 140 mg)	840 mg (6 X 140 mg)
Dose De-escalation level 1	420 mg (3 X 140 mg)	700 mg (5 x 140 mg)
Dose De-escalation level 2	280 mg (2 X 140 mg)	560 mg (4 X 140 mg)

Intrasubject Escalation is not allowed in this study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

- **Tests to be performed day 1 of each cycle of ibrutinib:**
  - History and physical exam
  - ECOG Performance Status
  - CBC
  - Comprehensive metabolic panel (Na, K, Cl, CO2, BUN, Creatinine, total bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)
  - LDH
  - Quantitative EBV-PCR (day 1 of cycle 1 and cycle 2). If quantitative EBV-PCR is positive on day 1 of cycle 2, then continue to monitor quantitative EBV-PCR on day 1 of subsequent cycles.
- **Blood Samples for ITK occupancy studies (to be processed for PBMCs):** cycle 1 day 1 predose and 4 hours post-dose; cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose; and cycle 2 day 1 (predose).
- **Blood Samples for Serum Cytokine levels (to be processed for serum):** cycle day 1 (predose) and cycle 2 day 1.
- **Blood Samples for pPLCγ1-Tyr783 phosphoflow analysis (to be processed for PBMCs):** day 1 (predose) and day 8 (predose) of cycle 1.
- **Blood Samples for T-cell subsets (to be processed for PBMCs):** cycle 1 day 1 (predose) and day 8 (predose), and cycle 2 day 1 (predose).
- **Blood Samples for Ibrutinib PK (to be processed for plasma):** cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose;.

Investigators and patients should make every effort to obtain blood samples for ITK occupancy studies and cytokine levels at appropriate specified time points. However, a window of +/- 3 days will be allowed if extenuating circumstances arise. If a patient terminated study treatment due to progression or other reasons, they may have research labs drawn at the end of study treatment visit per investigator discretion.

- **Tumor biopsy on day 8 (biopsy window between days 3 and 28):**

  For patients with CTCL, baseline and post-treatment day 8 biopsy (skin punch biopsies in MF patients or peripheral blood in Sezary patients) will be mandatory.

  For PTCL patients with cutaneous lesion(s), baseline and post-treatment day 8 biopsies (skin punch biopsy) will be mandatory.

  For PTCL patients with bone marrow involvement, if informed consent is provided by the patient, baseline and post-treatment day 8 bone marrow biopsy may be performed.

  For PTCL patients with other sites of involvement (i.e. lymph node or organ), no biopsies will be performed while on ibrutinib therapy due to increased risk of bleeding associated with needle or excisional biopsies.

  Investigators and patients should make every effort to obtain post-treatment biopsy on day 8, however it is acceptable if tumor biopsy is obtained between days 3-28 if extenuating circumstances arise.

- **Tests to be performed after completion of 2, 4, 6, 9, 12 cycles of ibrutinib (cycles are every 28 days +/- 3 days window)**
    - FDG-PET/CT obtained prior to next cycle of ibrutinib. In CTCL patients, CT scans alone are acceptable. In CTCL patients with skin only disease at baseline, CT will only need to be repeated if a patient achieves a CR in the skin to confirm absence of systemic progression.

Study Evaluation Schedule

Procedure	Screening	Cycle 1 28-day cycle		Cycle 2 and beyond 28-day cycle (+/- 3 days)		End of study
		Day **1**	Day **8** (window day 3 -28)	Day **1**	End of cycle	
Physical examination	X	X		X		X
ECOG performance status	X	X		X		X
ITK Occupancy Test		X[5]	X[5]	X (only cycle 2)[5]		X[4]
Serum Cytokine Test		X		X (only cycle 2)		X[4]
pPLCγ1-Tyr783 phosphoflow Test		X	X			X[4]
T-cell subsets		X	X	X (only cycle 2)		X[4]
Tumor biopsy	X		X (mandatory for CTCL, optional for PTCL)			
Hematology	X	X		X		X
LDH	X	X		X		X
Electrolytes	X	X		X		X
Quantitative EBV PCR		X		X[1]		
Pregnancy testing	X					
Ibrutinib (daily)[2]		X	X	X	X	
Ibrutinib PK			X (only cycle 1)[6]			
Disease/Response assessment	X				X[3]	

[1] If quantitative EBV PCR is positive on day 1 cycle 2, then continue to check EBV PCR on day 1 of each subsequent cycle.
[2] Ibrutinib is taken daily continuously in 28-day cycles.
[3] Disease response assessment at time points previously described (cycles 2, 4, 6, 9, 12, and thereafter approximately every 6 months at the physician's discretion).
[4] Per investigator decision (see section 10.0).
[5] ITK Occupancy Test will be collected cycle 1 day 1 predose and 4 hours post-dose; cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose; and cycle 2 day 1 (predose).
[6] Ibrutinib PK will be collected on Cycle 1 Day 8: predose, 1 hour, 2 hours, and 4 hours post-dose.

- **Tests after completion of 12 months of therapy at the physician discretion**
    - Clinical evaluation every 6 months (+/- 1 month).
    - CT chest, abdomen, pelvis every 6 months (+/- 1 month)

11.0 TOXICITIES/SIDE EFFECTS

See background section 3.2 for detailed discussion of Ibrutinib toxicities and side effects based on prior clinical experience. Also see protection of human subjects section 17.0 for detailed description of toxicities and side effects.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression of disease will be evaluated in this study using the revised response criteria for malignant lymphoma with incorporation of PET/CT.[33] Response in subjects with CTCL will be assessed using a specific skin scoring system with mSWAT and incorporation of measurements of extracutaneous disease as previously described.[36]

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 15 mm with conventional techniques (PET, CT, MRI, x-ray). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 15 mm), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphoma cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

12.1 Extracutaneous Response Criteria

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

12.2 Cutaneous T-cell Lymphoma (CTCL) Response Criteria

Dermatologic responses will be determined by the modified Severity-Weighted Assessment Tool (mSWAT), a standardized approach to measuring the extent and severity of overall skin disease in patients with CTCL. It will be briefly described and full details are provided in Appendix 3.[34] In addition, the response criteria for Sezary syndrome is also briefly described here and full details are provided in Appendix 3.[34] The purpose of this description is to optimize intra-observer objectivity and to minimize the potential for intra-observer and inter-observer variability in the measurement of overall skin disease. Only physicians who received training will be permitted to conduct mSWAT assessments during the clinical study. It is essential that physicians adhere as closely as possible to the prescribed procedures so as to reduce measurement error and variability. All efficacy assessments should be performed by the same physician for each patient whenever possible. Physicians will be instructed not to examine previous mSWAT assessments and full body photographs prior to conducting the current mSWAT assessment.

1. Total Body Surface Area (TBSA) Involvement by Skin Disease

The body is divided into 12 regions with pre-assigned %TBSA based on the literature of burn patients. The extent of skin disease in each region is quantified by using the patient's palm to measure the %TBSA involvement within region: patient's palm with 4 fingers (excluding the thumb) is 1% of TBSA. Patient's palm without fingers is 0.5% of TBSA. The patient's palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient's palm should be used in all mSWAT assessments during the course of the clinical study. The transparency will be labeled with the patient's study ID number kept in the patient's study file on site. Using the

baseline visit transparency of the patient's palm, the investigator will measure and record on the case report form (Example of table from CRF is given below) the %TBSA for each lesion type within each of the 12 regions.

2. Severity Weighting Factor

The severity weighting factors will be the following:

1= patch (flat erythema or erythema with mild infiltration)

2=plaque (elevated erythema or erythema with moderate infiltration)

4= tumor or ulceration (erythema with fissuring, ulceration or tumor)

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥5 mm is a tumor.

3. Calculating Skin Scores

The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques and tumors) within each region cannot exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0-7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBS of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400.

Region	% TBSA for the region	% TBSA Patch (or flat erythema)	% TBSA Plaque (or elevated/indurated erythema)	% TBSA Tumor/ Ulceration (or erythema w/fissuring, ulceration)
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
% BSA by category	100			
Severity Weighting Factor		X 1	X 2	X 4
Skin Score Subtotal				

Responses will be determined by the criteria described in the table below. Progression of disease while on treatment should be confirmed by a second assessment 1-4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely. A second mSWAT is only required for cutaneous patients where mSWAT is the only response assessment demonstrating disease progression (if POD by alternate test (PET, peripheral blood, etc), a repeat mSWAT is unnecessary).

Description	Status
No evidence of disease; 100% improvement	CR
Greater than or equal to 50% decrease in skin scores compared to baseline and improvement is maintained for 4 weeks	PR
Less than 50% decrease in skin scores compared to baseline	SD
≥25% increase in skin scores compared to baseline while the patient is actively taking study drug -OR- ≥50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patent is actively taking the study drug.	PD

Response Criteria for Sezary Syndrome

Classification of Blood Involvement in TNMB Staging System

Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Response in Blood

Table 9. Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL[36] or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to $\geq B_1$ in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*As determined by absolute numbers of neoplastic cells/μL.
†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
§Whichever occurs first.

12.3 Study Endpoints

- Overall response rate is the sum of the complete and partial response rates.
- Duration of response is calculated from the date of initial documentation of a response to the date of first documented evidence of disease progression, relapse, or death.
- Progression free survival is defined as duration of time from initiation of therapy to disease progression, death, or last follow-up.
- Event free survival is defined as duration of time from initiation of therapy to failure of treatment including any disease progression, early discontinuation of protocol treatment for any reason, initiation of new treatment without documented progression, death as a result of any cause, or last follow-up.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Treatment will continue until the occurrence of any of the following events.

- Disease progression (confirmed by 2 assessments in CTCL patients)
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of ibrutinib for any reason.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Pregnancy or a positive pregnancy test

14.0 BIOSTATISTICS

This is a phase I study that will use a modified 3+3 dose escalation scheme to determine the maximum tolerated dose (MTD) of ibrutinib. The primary and secondary objectives of the study are defined in Section 2.0. DLT is defined in Section 4.1.3. The modified 3+3 dose-escalation scheme for this study is as follows. Patients will be accrued to the study in cohorts of 3 (starting with dose level 1). For any given dose an initial cohort of 3 patients will be treated at that dose. If more than one DLT was observed among the 3 patients, stop and de-escalate to dose level -1, or declare the previous dose level as MTD if it had already been tested using 6 patients. If zero or one DLT is observed, an additional cohort of 3 patients will be treated at that dose. The dose will be escalated if at most one DLT was observed among the total of 6 patients. If at least two DLTs were observed among the total of 6 patients, stop and de-escalate to dose level -1, or declare the previous dose level as MTD if it had already been tested using 6 patients. The reason of using this modified design is to ensure that dose level 1 and dose level 2 can have 6 patients for comparison of efficacy (see below) if they are equally toxic (i.e., both have 0 or 1 DLT). For this design the probability of escalation is as follows.

True toxicity rate	5%	10%	15%	20%	25%	30%	40%
Prob. of escalation	0.967	0.886	0.776	0.655	0.534	0.420	0.233

The maximum number of patients needed for this dose escalation design is 12. Accrual is expected to be 24 patients per year subject to the waiting period of 1 month for determining DLT for the current dose level. If either dose level 1 and dose level 2 showed either 0 or 1

DLT, the dose level with evidence of the higher level of preliminary efficacy, defined as the overall response rate within the first two cycles, will be declared MTD. If both dose levels are equally toxic AND efficacious, then dose level 1 will be declared MTD.

At the established MTD, an additional 12 patients will be enrolled into an expansion cohort. An equal number of CTCL and PTCL patients will be treated at the MTD dose. The reason for enrolling this additional cohort is to increase the number of patients at the MTD in order to obtain better estimates for efficacy. However, in the unlikely event that more than 3 DLTs were observed in this expansion cohort, we will halt the enrollment for patients' safety protection, and all treatment-related toxicities will be thoroughly reviewed by investigators. If it is deemed that the current MTD is actually too toxic, the protocol will be amended at the discretion of the study investigators to enroll further patients at a lower dose level. Given the differences in clinical presentation and disease biology between CTCL and PTCL, we will also preliminarily estimate efficacy and toxicity in the CTCL and PTCL patients separately.

To address secondary objectives, the complete and partial response rates will be estimated by sample proportions and confidence intervals using exact binomial methods for each dose level (the non-MTD dose level will have a small sample size so the associated confidence interval will be wide). Progression free survival, event free survival and duration of response in responders will be assessed using Kaplan-Meier methods. Percentage ITK-occupancy at different dose levels will be summarized. Comparisons of cytokine markers, T-cell subsets, and pPLCγ1 levels before and after treatment with ibrutinib will be performed using paired t-tests. Note that there will be multiple such tests due to the repeated measurements of such quantities. Expression of GATA3 and TBX1 by immunohistochemistry will be correlated with patient response by Fisher's exact test. Gene expression profiles before and after treatment with ibrutinib will be summarized using descriptive statistics.

This is a multi-center study, including the following sites: MSK and Ohio State University. Data collected from all centers will be analyzed at MSK.

14.2 Definition of Evaluable Patients

1. Evaluable for phase I dose-escalation: only those participants who have received at least one cycle of therapy.
2. Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 For Participating Sites:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center.

To complete registration and enroll a participant from another institution, the participating site must contact the MSK study coordinator to notify him/her of the participant registration. Registration documents should be submitted to the Multicenter Trial Core Coordinator at medmctcore@mskcc.org.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist.
- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing , the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site is in good standing, the MSK research staff will send the completed registration documents to the MSK PPR Office for participant enrollment as stated in section 15.1.

Once the participant is registered, the participant will be assigned a number in the MSK Clinical Research Database (CRDB). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

There is no randomization in this study.

16.0 DATA MANAGEMENT ISSUES

A MSKResearch Study Assistant (RSA) will be assigned to the study. The responsibilities of the MSKRSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Data to be collected will include:

1. Patient demographics and related features:
   - age
   - sex
2. Disease related features:
   - history of disease (including staging) and prior treatments
   - results of all tests related to the study
   - disease status at long-term follow-up
3. Treatment related
   - duration of treatment
   - response to treatment
   - toxicities of treatment

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based system, Clinical Research Database CRDBi Multicenter. Data entry guidelines have been generated for this study and site staff will receive database training prior to enrolling its first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in **Table 1** below.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Toxicities/adverse events that meet study reporting requirements not previously submitted with SAE Reports
- Response designation
- Any other forms of source docuementation required per protocol

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into CRDBi Multicenter). Source documentation should be sent to MSK at the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

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16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSK according to chart.

Table 1 : Data and Source Documentation Timeline

Time point	Data	Source Documentation
Baseline	Within **24 hours** of consent (see section 15.1.1)	Within **24 hours** of consent (see section 15.1.1)
Study Visits	Within **14 days** of the study visit	Within **14 days** of the study visit
Serious Adverse Events	Within **3 days** of event (see section 17.3) Updates to be submitted as available	Within **3 days** of event (see section 17.3

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSK will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSK research staff twice a month.

Participating sites should respond to queries within 14 days of receipt.

16.1 Quality Assurance

Registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Retention of Records: All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be retained for at least 3 years after the investigation is completed.

16.1.1 Quality Assurance for Participating Sites

Quality Assurance will be conducted according to MSK guidelines and Multicenter ` SOPs.

Research staff at MSK will conduct periodic reviews of regulatory documentation, protocol compliance and data, and issue queries as appropriate. The level and frequency of monitoring or auditing may be adjusted based on ongoing site performance.

16.1.2 Response Review

All sites participant's responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form and HIPAA authorization
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical licenses for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators, consenting professionals and key study personnel at the participating site
- Documentation of Good Clinical Practice training for the participating site PI and co-PI
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.

Each participating site must obtain IRB approval for all amendments within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

16.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations
A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events should be reported according to sections 17.4.1 and 17.3 of this protocol.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations
Deviations to the research protocol that involve patient eligibility, an informed consent procedure change, and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites should contact the MSK PI who will in turn seek approval from the MSK IRB/PB.

Retrospective Deviations
Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations should be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting
Participating sites should report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations should be submitted to MSK upon receipt.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of official site IRB correspondence , including approvals and acknowledgements, to MSK.

16.4 Document maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to fully document protocol implementation and allow data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an onsite regulatory binder and sent to MSK as outlined within the protocol. The regulatory binder on site will be reviewed by the MSK designated study monitor at monitoring visits. A regulatory binder for each participating site will also be maintained at MSK within the institution's Protocol Information Management System (PIMS).

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years

16.5 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolve.

17.0 PROTECTION OF HUMAN SUBJECTS

Potential Risks

There are limited treatment options available for patients with relapsed and refractory PTCL and CTCL. The toxicities associated with ibrutinib are generally mild and reversible. The long-term toxicities of ibrutinib are not well-described as it is a relatively new agent.

- The most common effects, occurring in one of every 3-4 patients have been:

  Diarrhea

  Tiredness (Fatigue)

  Nausea

  Infection

- Other side effects that have been seen in one of every 5-10 patients include:

  Cough

  Swelling of the hands or feet (Peripheral edema)

  Rash

  Common cold (Upper respiratory infection)

  Fever

  Dizziness

  Constipation

  Joint aches (Arthralgia)

  Bruises (contusion)

  Headache

  Muscle aches (Myalgia)

  Shortness of breath (dyspnea)

  Vomiting

  Stomach pain (Abdominal pain)

  Muscles cramps (Muscle spasms)

Decreased appetite

Indigestion/heartburn (Dyspepsia)

Low red blood cells count (Anemia)

Low platelets, cells that help blood to clot (Thrombocytopenia)

Low white blood cells, cells that help fight infection (Neutropenia)

Muscle and join pain (musculoskeletal pain)

Sores in the mouth (stomatitis)

Sinus infection (sinusitis)

Urinary tract infection

Back pain

Pain in extremity

Small red or purple spots caused by bleeding under the skin (Petechiae)

Most of these side effects have been mild to moderate in severity, however severe side effects have occurred. Some side effects have been severe enough to lead to hospitalization, disability and sometimes death.

- The severe side effects, seen in one of every 11-100 patients include:

  Not having enough fluids (Dehydration)

  Low white blood cells with fever (Febrile neutropenia)

  Abnormal heart rhythm (Atrial fibrillation)

  Bleeding around the brain (Subdural hematoma)

  Excess fluid in the lining of the lungs (Pleural effusion)

  Acute kidney injury (Acute renal failure)

  Increased level of uric acid in the blood (Hyperuricemia)

  Decreased level of potassium in the blood (Hypokalemia)

  Fainting (Syncope)

  Pneumonia

  Feeling weak (Asthenia)

  Nose bleed (Epistaxis)

  Increase in while blood cell counts (Lymphocytosis and/or Leukocytosis)

  High blood pressure (hypertension)

- Rare serious side effects (less than 1 in 100 patients) that you should know about are:

  Blurry Vision

  Skin infection

Severe infection through the body (sepsis)

Failure of the lungs to function properly (respiratory failure)

Stroke with bleeding in the brain (Cerebrovascular accident with hemorrhage)

Colon inflammation with bleeding (Hemorrhagic colitis)

Low levels of all types of blood cells -white blood cells, red blood cells and platelets

(Pancytopenia)

Enlarged spleen (Splenomegaly)

Inflammatory state of the whole body (Systemic inflammatory response syndrome)

Tumor lysis syndrome (TLS)

Events of Special Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by Pharmacyclics. These events will be reported to Pharmacyclics within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

Pregnancy

All initial reports of pregnancy must be reported to Pharmaycyclics by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported in a timely fashion. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event. using the CRDB SAE Report Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Prohibitions and Restrictions

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Potential Benefits

There are limited treatment options available for patients with relapsed and refractory PTCL and CTCL, and outcomes for this patient population are generally poor. Ibrutinib is being studied in this patient population to investigate whether this therapy demonstrates efficacy as a single agent. Pharmacyclics is supplying ibrutinib free of charge.

Provisions for preventing and treating adverse events

Assessment for treatment-related toxicities will occur at every cycle. Management of toxicities will be in accordance with standard medical practices employed at MSK and the participating sites.

Patients will receive standard anti-emetics as prophylaxis against nausea and vomiting.

Alternatives/Options for treatment

For patients eligible, alternative therapeutic options would include pralatrexate, vorinostat, romidepsin, and enrollment on alternative clinical trial with an investigational agent.

Costs

The patient will be responsible for all costs related to treatment and complications of treatment, including all hospitalizations.

Ibrutinib will be supplied by Pharmacyclics free of charge. The patient will not be responsible for the cost of correlative studies.

Participation in this study is voluntary and patients will not be paid for participation.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research

Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE

- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Reporting by MSK to Pharmacyclics

- **Reporting Timeframe:** The MSK PI must inform Pharmacyclics Drug Safety via email at the contact information listed below.

Pharmacyclics Drug Safety and Pharmacovigilance

Contact Information:

Email: drugsafety@pcyc.com

- **Reporting Forms:** The MSK PI will report such SAEs using the CRDB SAE Report Form.

SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

- **Reporting Period:** The reportable events that are subject to this provision are those that occur from the start of administration of the first dose of the Product through thirty (30) days after discontinuation of the Product. SAEs occurring prior to the first dose of the Product but after signature of the ICF and more than thirty (30) days after discontinuation of the Product that are assessed by the Investigator as related to the Product should also be reported.

- **Follow-up Information:** The MSK PI will assist Pharmacyclics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

- **Regulatory Reporting:** Reporting an SAE to Pharmacyclics does not relieve the MSK PI of the responsibility for reporting it to the FDA, local regulatory authority, or IRB/IEC as required.

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their site IRB per local guidelines. Site IRB approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report form to MSK within 3 calendar days of learning of the event.

- When a life- thereatening event or death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

Responsibilities of MSK

- MSK is responsible for submitting all SAEs to the MSK IRB/PB and Pharmacyclics as described in the protocol.
- MSK is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 15 days of receiving the stamped SAE report from the MSK IRB/PB.
- MSK is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

SAE contact information for the Coordinating Center is listed below:

Multicenter Trials Core Staff
MSK Clinical Trials Office
(E) medmctcore@mskcc.org

Anita Kumar, MD
Memorial Sloan Kettering Center
Email: kumara2@mskcc.org
(O) 212-639-2668

17.4 Safety Reports

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. All outside safety reports will be made available to the participating sites. Outside safety reports that are reportable to the MSK IRB/PB will be distributed to the participating sites immediately upon receiving a stamped copy from the MSK IRB/PB. Participating sites will receive a special alert for any outside safety reports that warrant a significant change to the conduct of the study. Outside safety reports that are not reportable to the MSK IRB/PB, will be sent to the participating sites monthly.

Participating sites are responsible for submitting safety reports to their site IRB per their local guidelines. All site IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

17.4.1 Unanticipated Problems

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **and**
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); **and**
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs should be reported to MSK via SAE Report form as per section 17.3 of this protocol. All other UPs should be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
- The name of the investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the partcipant's medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

1. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(25)**:** 4124-4130. doi: 10.1200/JCO.2008.16.4558

2. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S *et al.* Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(31)**:** 4730-4739. doi: 10.1200/JCO.2009.27.7665

3. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B *et al.* Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(9)**:** 1182-1189. doi: 10.1200/JCO.2010.29.9024

4. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M *et al.* Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(6)**:** 631-636. doi: 10.1200/JCO.2011.37.4223

5. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T *et al.* Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(18)**:** 2190-2196. doi: 10.1200/JCO.2011.38.0402

6. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH *et al.* Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(16)**:** 1970-1976. doi: 10.1200/JCO.2012.44.7524

7. Buggy JJ, Elias L. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. *International reviews of immunology* 2012; **31**(2)**:** 119-132. doi: 10.3109/08830185.2012.664797

8. Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B *et al.* The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proceedings of the National Academy of Sciences of the United States of America* 2010; **107**(29)**:** 13075-13080. doi: 10.1073/pnas.1004594107

9. Advani RH, Buggy JJ, Sharman JP, Smith SM, Boyd TE, Grant B *et al.* Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(1)**:** 88-94. doi: 10.1200/JCO.2012.42.7906

10. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS *et al.* Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *The New England journal of medicine* 2013. e-pub ahead of print 2013/06/21; doi: 10.1056/NEJMoa1306220

11. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *The New England journal of medicine* 2013; **369**(1)**:** 32-42. e-pub ahead of print 2013/06/21; doi: 10.1056/NEJMoa1215637

12. de Rooij MF, Kuil A, Geest CR, Eldering E, Chang BY, Buggy JJ *et al.* The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. *Blood* 2012; **119**(11)**:** 2590-2594. doi: 10.1182/blood-2011-11-390989

13. Pan Z, Scheerens H, Li SJ, Schultz BE, Sprengeler PA, Burrill LC *et al.* Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. *ChemMedChem* 2007; **2**(1)**:** 58-61. doi: 10.1002/cmdc.200600221

14. Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y *et al.* Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood* 2013; **122**(15)**:** 2539-2549. doi: 10.1182/blood-2013-06-507947

15. Siliciano JD, Morrow TA, Desiderio SV. Itk, a T-Cell-Specific Tyrosine Kinase Gene Inducible by Interleukin-2. *Proceedings of the National Academy of Sciences of the United States of America* 1992; **89**(23)**:** 11194-11198. doi: DOI 10.1073/pnas.89.23.11194

16. Schaeffer EM, Yap GS, Lewis CM, Czar MJ, McVicar DW, Cheever AW *et al.* Mutation of Tec family kinases alters T helper cell differentiation. *Nature immunology* 2001; **2**(12)**:** 1183-1188. doi: 10.1038/ni734

17. Andreotti AH, Schwartzberg PL, Joseph RE, Berg LJ. T-cell signaling regulated by the Tec family kinase, Itk. *Cold Spring Harbor perspectives in biology* 2010; **2**(7)**:** a002287. e-pub ahead of print 2010/06/04; doi: 10.1101/cshperspect.a002287

18. Linka RM, Risse SL, Bienemann K, Werner M, Linka Y, Krux F *et al.* Loss-of-function mutations within the IL-2 inducible kinase ITK in patients with EBV-associated lymphoproliferative diseases. *Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K* 2012; **26**(5)**:** 963-971. doi: 10.1038/leu.2011.371

19. Huck K, Feyen O, Niehues T, Ruschendorf F, Hubner N, Laws HJ *et al.* Girls homozygous for an IL-2-inducible T cell kinase mutation that leads to protein deficiency develop fatal EBV-associated lymphoproliferation. *The Journal of clinical investigation* 2009; **119**(5)**:** 1350-1358.

20. Fowell DJ, Shinkai K, Liao XC, Beebe AM, Coffman RL, Littman DR *et al.* Impaired NFATc translocation and failure of Th2 development in Itk-deficient CD4+ T cells. *Immunity* 1999; **11**(4)**:** 399-409.

21. Schwartzberg PL, Finkelstein LD, Readinger JA. TEC-family kinases: regulators of T-helper-cell differentiation. *Nature reviews. Immunology* 2005; **5**(4)**:** 284-295. e-pub ahead of print 2005/04/02; doi: 10.1038/nri1591

22. Schaeffer EM, Debnath J, Yap G, McVicar D, Liao XC, Littman DR *et al.* Requirement for Tec kinases Rlk and Itk in T cell receptor signaling and immunity. *Science* 1999; **284**(5414)**:** 638-641. e-pub ahead of print 1999/04/24;

23. Guo W, Liu R, Ono Y, Ma AH, Martinez A, Sanchez E *et al.* Molecular characteristics of CTA056, a novel interleukin-2-inducible T-cell kinase inhibitor that selectively targets malignant T cells and modulates oncomirs. *Molecular pharmacology* 2012; **82**(5)**:** 938-947. doi: 10.1124/mol.112.079889

24. Shin J, Monti S, Aires DJ, Duvic M, Golub T, Jones DA *et al.* Lesional gene expression profiling in cutaneous T-cell lymphoma reveals natural clusters associated with disease outcome. *Blood* 2007; **110**(8)**:** 3015-3027. doi: 10.1182/blood-2006-12-061507

25. Dubovsky JA BK, Woyach JA, et al. Ibrutinib is an irreversible molecular inhibitor of interleukin-2 inducible kinase: expanding therapeutic potential and modulating a Th1 selective pressure in CD4 T-cells. In: *American Society of Hematology Annual Meeting 2012*. Atlanta, GA, 2012.

26. Miyagaki T, Sugaya M, Fujita H, Ohmatsu H, Kakinuma T, Kadono T *et al.* Eotaxins and CCR3 interaction regulates the Th2 environment of cutaneous T-cell lymphoma. *The Journal of investigative dermatology* 2010; **130**(9)**:** 2304-2311. doi: 10.1038/jid.2010.128

27. Yoshie O, Fujisawa R, Nakayama T, Harasawa H, Tago H, Izawa D *et al.* Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. *Blood* 2002; **99**(5)**:** 1505-1511.

28. Di Renzo M, Rubegni P, De Aloe G, Paulesu L, Pasqui AL, Andreassi L *et al.* Extracorporeal photochemotherapy restores Th1/Th2 imbalance in patients with early stage cutaneous T-cell lymphoma. *Immunology* 1997; **92**(1)**:** 99-103. e-pub ahead of print 1997/11/26;

29. Guenova E, Watanabe R, Teague JE, Desimone JA, Jiang Y, Dowlatshahi M *et al.* TH2 Cytokines from Malignant Cells Suppress TH1 Responses and Enforce a Global TH2 Bias in Leukemic Cutaneous T-cell Lymphoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013. e-pub ahead of print 2013/06/21; doi: 10.1158/1078-0432.CCR-12-3488

30. Hahtola S, Tuomela S, Elo L, Hakkinen T, Karenko L, Nedoszytko B *et al.* Th1 response and cytotoxicity genes are down-regulated in cutaneous T-cell lymphoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2006; **12**(16)**:** 4812-4821. e-pub ahead of print 2006/08/18; doi: 10.1158/1078-0432.CCR-06-0532

31. McQuillan A, Dotti S, Cristiano A, Ferrari M, Razzuoli E, Amadori M. Evaluation of a robotic system for the recovery of peripheral blood mononuclear cells. *Biologicals : journal of the International Association of Biological Standardization* 2012; **40**(1)**:** 31-35. e-pub ahead of print 2011/10/22; doi: 10.1016/j.biologicals.2011.09.009

32. Felices M, Berg LJ. The Tec kinases Itk and Rlk regulate NKT cell maturation, cytokine production, and survival. *J Immunol* 2008; **180**(5)**:** 3007-3018.

33. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ *et al.* Revised response criteria for malignant lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007; **25**(5)**:** 579-586. e-pub ahead of print 2007/01/24; doi: 10.1200/JCO.2006.09.2403

34. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR *et al.* Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(18)**:** 2598-2607. doi: 10.1200/JCO.2010.32.0630

20.0 APPENDICES

Appendix 1: ITK occupancy assay

Appendix 2: Investigator's Brochure

Appendix 3: Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer.[34]

Appendix 4: A list of common CYP3A inhibitors or inducers

Appendix 5: Pill Diary

Appendix 6: Correlative Studies

Appendix 7: Guideline for Banking Skin Punch Biopsies in HOT-B

Appendix 8: PBMC and Plasma Collection Timepoints

Appendix 9: Laboratory Manual

Appendix 4: Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5 are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Refer to Section 9.2.3 on instructions for concomitant use of CYP3A4/5 inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A4/5	
Strong inhibitors:	**Moderate inhibitors:**
Carbamazepine INDINAVIR Efavirenz NELFINAVIR Nevirapine RITONAVIR Barbiturates CLARITHROMYCIN Glucocorticoids ITRACONAZOLE Modafinil KETOCONAZOLE Oxcarbarzepine NEFAZODONE Phenobarbital SAQUINAVIR Phenytoin TELITHROMYCIN Pioglitazone	Rifabutin aprepitant Rifampin erythromycin St. John's Wort diltiazem Troglitazone fluconazole grapefruit juice Seville orange juice verapamil **Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl

Inducers of CYP3A4/5 -	
dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone	norfloxacin norfluoxetine star fruit telaprevir troleandomycin voriconazole

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix 5: Pill Diary

A Multicenter Phase I Study of Ibrutinib in Relapsed and Refractory T-cell Lymphoma

Patient Name: _____ Study ID: _____MRN:_____

Number of Pills Given:_____ Pill Bottle(s) returned: Circle **Yes** or **No**

Total Daily Dose:_____ Number of Pills **returned**:_____

(To be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

SPECIAL INSTRUCTIONS

1. Take Ibrutinib by mouth every morning at about the same time with a full glass (8 ounces) of water (**avoid taking ibrutinib with grapefruit or Seville orange juice**).
2. The capsules should be swallowed intact. Please do not open the capsules, chew or dissolve them in water.
3. If a dose is missed, it can be taken as soon as possible on the same day. Return to the normal schedule the following day.
4. Please do not take extra capsules to make up a missed dose.

CYCLE #: _____ # of WEEKS_____

Day	Date	Time	Number of 140 mg capsules of Ibrutinib taken
Example	1/1/2011	9:00 AM	4
1			
2			
3			
4			
5			
6			
7			
8			
9			

10			
11			
12			
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25			
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28			

Patient Signature: _____ **Date:** _____

Consenting Professional/Research RN Signature:
_____ **Date:** _____

Comments: _____

Appendix 6: Correlative Studies

SAMPLES	COLLECTION TIMEPOINT	SAMPLE COLLECTION VIAL	PROCESSING	SHIPPING	PURPOSE
Plasma	Cycle 1 Day 8: predose, 1hr, 2 hrs, and 4 hrs post-dose	- Sodium heparin tube (green top	-Processing per Appendix 1 within 1 hr of collection	-Ship to Frontage lab on dry ice	- Pharmacokinetics (PK) analysis
PBMCS	Cycle 1: day 1 predose and 4 post-dose **and** day 8 predose, 1, 2, and 4 hrs post-dose Cycle 2: day 1	-CPT tube	-None	-Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs)	-ITK occupancy -Other correlative studies (i.e. phosphoflow, T-cell subsets, etc)
Serum	Cycle 1: day 1 Cycle 2: day 1	-Red top tube (Serum separator tube (SST))	-None	- Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSKCC (Mon-Thurs)	-Serum cytokine analysis
Skin Biopsy	Cycle 1: day 1 **and** day 8	-FFPE slides or tissue block	-Per standard clinical pathology guidelines	- Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs)	-IHC and GEP studies
Tissue banking **(Optional)**	Baseline biopsy	-FFPE slides or tissue block	-Per standard clinical pathology guidelines	- Ship ambient to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs) at the end of the study	-Biomarkers for response (i.e. genomic sequencing)

MSKCC STANDARD OPERATING PROCEDURE
Hematologic Oncology Divisional Tissue Bank
James W. Young, MD, Laboratory Director

Document:

Cryopreservation of skin punch biopsy	
Effective Date:	01 April 2013
Supersedes:	05 July 2012
Reference:	Jim Krueger's (212-327-7730) Lab, RU; Artemis Khatcherian (212-327-8334)

OBJECTIVE AND SCOPE:

This procedure describes the method for freezing (cryopreservation) of skin biopsy samples (punch biopsies) en bloc for later study, usually by immunohistochemistry. All activities will be performed in the Hematologic Oncology Divisional Tissue Bank under clean and sterile conditions as indicated.

If a portion of this skin biopsy will be placed in formalin, you must first cut the biopsy in half, full thickness, with preservation of epidermis and dermis, and place half in formalin. Then proceed with freezing of the other half. In lieu of taking one larger punch biopsy and splitting it in two, it is usually easier to take two smaller punch biopsies from immediately adjacent sites and process one in formalin and the other by cryopreservation. Each small punch biopsy requires a single suture or even a butterfly bandage, whereas a larger punch biopsy usually requires two sutures.

The punch biopsies will have been obtained under sterile technique. All subsequent processing of the specimens, however, will be performed under clean but not sterile conditions using universal precautions.

2.0 MATERIALS AND REAGENTS:

2.1. Plastic "boats" for freezing tissue (CRYO MOLD, Standard; 25 x 20 x 5 mm, Cat #62534-25, 100/pk, Electron Microscopy Sciences, PO Box 550, 1560 Industry Road, Hatfield, PA 19440, tel 215-412-8400; FAX 215-412-8450; www.emsdiasum.com. Manufactured for Sakura Finetek USA, Inc. Torrance, CA 90501: "Tissue-Tek" #4557)

2.2. OCT compound (Optimal Cutting Temperature Compound, "Tissue-Tek" #4583, manufactured for Sakura Finetek USA, Inc. Torrance, CA 90501)

2.3. Dry ice in 100% ethanol alcohol bath
2.4. Forceps
2.5. Label(s), markers made for -70^{o}C freezing

3.0 PROCEDURE:

3.1. Print label from CRDB and attach to plastic boat so that patient name and MRN are visible from above
3.2. Prepare a small plastic bag by writing in freezing markers the intended box location (you may also want to open it in the hood for ease of transfer after freezing)
3.3. Mark label with "E" and place skin biopsy in the boat so that the **E**pidermis is oriented toward that end (look for hair cell protrusions for orientation).
3.4. With the skin tissue in the boat on the bench surface at RT, add the OCT from the outside circumference, gradually working inward toward the tissue. Cover approximately to the lower internal ledge of the boat.
3.5. Grasp the boat with locked forceps on the labeled end. Using tweezers to level the other side, lower the boat with the skin in OCT into a slurry of dry ice in 100% ethyl alcohol. Be very careful NOT to allow any of the alcohol to get into the OCT with the skin
3.6. Hold the boat partially submerged until the OCT is no longer transparent and appears solidified. This process should begin from the bottom and proceed inward from the edges.
3.7. When completely frozen place in plastic freezer bag and transfer directly to -80 freezer

Approved by: (print name)	**Divn./Dept.**	**Signature**	**Date**
James W. Young, MD	HOTB Laboratory Director		

Appendix 8: PBMC and Plasma Collection Timepoints

PBMC AND PLASMA COLLECTION TIMEPOINTS

Cycle	Time-Point	Non-Sezary	Sezary
C1D1	Pre-Dose	6 CPT Tubes, 1 red top tube	7 CPT Tubes, 1 red top tube
	4 Hours Post-Dose	1 CPT Tube	1 CPT Tube
C1D8	Pre-Dose	6 CPT Tubes, 1 Na Hep Tube	7 CPT Tubes, 1 Na Hep Tube
	1 Hour Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
	2 Hours Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
	4 Hours Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
C2D1	Pre-dose	4 CPT Tubes, 1 red top tube	4 CPT Tubes, 1 red top tube

Memorial Sloan Kettering Cancer Center

LABORATORY MANUAL

A Multicenter Phase I Study of Ibrutinib in Relapsed and Refractory T-cell Lymphoma

MSK IRB Study # 14-227

Principal Investigator: Anita Kumar

STUDY CONTACT LIST:

Name	Organization/Position	Contact Information	Reasons for Contact
Anita Kumar, MD	MSK, Lead Principal Investigator	Phone: 646-888-4184 Email:kumara2@mskcc.org	• Protocol deviation requests • Patient treatment requests, any other concerns
Lakeisha Lubin	MSK, MCT Research Project Coordinator	Phone: 646-888-1005 Email:LubinL@mskcc.org	• Study questions • Notification of shipments to MSK
Gianna McArthur	MSK, Research Study Assistant	Phone: 646-888-1004 Email: McarthuG@mskcc.org	• Study questions • Notification of shipments to MSK
Veenna Minnal	MSK, Research Study Assistant	Phone: 646-449-1316 Email: minnalv@mskcc.org	• Notification of shipments to MSK
Mira Hong	Frontage Laboratory	Mhong@frontagelab.com	• confirm shipment

OVERVIEW AND CORRELATIVE LIST:

We plan to perform exploratory biomarker analysis to gain insight into ibrutinib's mechanism of action in Peripheral T-cell lymphoma (PTCL) and to explore biomarkers that may predict treatment response.

The following samples are being obtained for protocol purposes, and are for the correlative studies: They are outlined in detail in protocol sections- 3.4 Rationale for Correlative Studies and 10.0 Evaluation During Treatment/ Intervention:

- **Peripheral Blood Mononuclear Cell (PBMC)**
- **Serum**
- **Plasma**
- **Skin Biopsy**
- **Tissue banking**

SAMPLE SUPPLIES FROM MSK

The following supplies will be provided by Memorial Sloan Kettering Cancer Center. The Institution should request a resupply of sample collection kits and allow 7 calendar days for delivery.

- Therapak insulated shippers
- Absorbent liners for shipping
- BD Vacutainer™ Glass Mononuclear Cell Preparation (CPT) Tubes
- Shipping label
- Sodium heparin tube (green top)
- Red top (Serum Separator Tube (SST))

Pre-printed UPS air bills for samples being shipped to MSK and Frontage Laboratories will be provided by the MSK study team.

Supply Re-order

All supply re-orders should be emailed to Lakeisha Lubin or Gianna McArthur at LubinL@mskcc.org and Mcarthug@mskcc.org. Please specify in the e-mail the specific supplies needed.

STUDY EVALUATION SCHEDULE

STUDY EVALUATION SCHEDULE						
Procedure	**Screening**	**Cycle 1** 28-day cycle		**Cycle 2 and beyond** 28-day cycle (+/- 3 days)		**End of study**
		Day **1**	Day **8** (window day 3 - 28)	Day **1**	**End of cycle**	
Physical examination	X	X		X		X
ECOG performance status	X	X		X		X
ITK Occupancy Test		X[5]	X[5]	X (only cycle 2)[5]		X[4]
Serum Cytokine Test		X		X (only cycle 2)		X[4]
pPLCγ1-Tyr783 phosphoflow Test		X	X			X[4]
T-cell subsets		X	X	X (only cycle 2)		X[4]
Tumor biopsy	X		X (mandatory for CTCL, optional for PTCL)			

Hematology	X	X		X		X
LDH	X	X		X		X
Electrolytes	X	X		X		X
Quantitative EBV PCR		X		X[1]		
Pregnancy testing	X					
Ibrutinib (daily)[2]		X	X	X	X	
Ibrutinib PK			X (only cycle 1)[6]			
Disease/Response assessment	X				X[3]	

[1] If quantitative EBV PCR is positive on day 1 cycle 2, then continue to check EBV PCR on day 1 of each subsequent cycle.

[2] Ibrutinib is taken daily continuously in 28-day cycles.

[3] Disease response assessment at time points previously described (cycles 2, 4, 6, 9, 12, and thereafter approximately every 6 months at the physician's discretion).

[4] Per investigator decision (see section 10.0).

[5] ITK Occupancy Test will be collected cycle 1 day 1 predose and 4 hours post-dose; cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose; and cycle 2 day 1 (predose).

[6] Ibrutinib PK will be collected on Cycle 1 Day 8: predose, 1 hour, 2 hours, and 4 hours post-do

SAMPLE COLLECTION

SAMPLES	COLLECTION TIMEPOINT	SAMPLE COLLECTION VIAL	PROCESSING	SHIPPING	PURPOSE
Plasma	Cycle 1 Day 8: predose, 1hr, 2 hrs, and 4 hrs post-dose	- Sodium heparin tube (green top	-Processing per Appendix 1 within 1 hr of collection	-Ship to Frontage lab on dry ice	- Pharmacokinetics (PK) analysis
PBMCS	Cycle 1: day 1 predose and 4 post-dose **and** day 8 predose, 1, 2, and 4 hrs post-dose Cycle 2: day 1	-CPT tube	-None	-Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs)	-ITK occupancy -Other correlative studies (i.e. phosphoflow, T-cell subsets, etc)
Serum	Cycle 1: day 1 Cycle 2: day 1	-Red top tube (Serum separator tube (SST))	-None	- Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSKCC (Mon-Thurs)	-Serum cytokine analysis
Skin Biopsy	Cycle 1: day 1 **and** day 8	-FFPE slides or tissue block	-Per standard clinical pathology guidelines	- Ship ambient same day to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs)	-IHC and GEP studies
Tissue banking **(Optional)**	Baseline biopsy	-FFPE slides or tissue block	-Per standard clinical pathology guidelines	- Ship to Hematologic Oncology Tissue Bank (HOTB) at MSK (Mon-Thurs)at the end	-Biomarkers for response (i.e. genomic sequencing)

				of the study	

Note: Investigators and patients should make every effort to obtain blood samples for ITK occupancy studies and cytokine levels at appropriate specified time points. However, a window of +/- 3 days will be allowed if extenuating circumstances arise. If a patient terminated study treatment due to progression or other reasons, they may have research labs drawn at the end of study treatment visit per investigator discretion.

PBMC AND PLASMA COLLECTION TIMEPOINTS

Cycle	Time-Point	Non-Sezary	Sezary
C1D1	Pre-Dose	6 CPT Tubes, 1 red top tube	7 CPT Tubes, 1 red top tube
	4 Hours Post-Dose	1 CPT Tube	1 CPT Tube
C1D8	Pre-Dose	6 CPT Tubes, 1 Na Hep Tube	7 CPT Tubes, 1 Na Hep Tube
	1 Hour Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
	2 Hours Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
	4 Hours Post-Dose	1 CPT Tube, 1 Na Hep Tube	1 CPT Tube, 1 Na Hep Tube
C2D1	Pre-dose	4 CPT Tubes, 1 red top tube	4 CPT Tubes, 1 red top tube

PLASMA:

SAMPLE COLLECTION TIME POINTS:

- **Blood samples for ibrutinib pharmacokinetic to be processed for plasma:** cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose
- Use 2mL **sodium heparin tube (green top).**

PROCESSING:

Frontage Labortory will perform bioanalysis managed by PCYC. Instruction for processing the Ibrutnib PK can be found in **Appendix 1-Pharmacokinetic Collection Manual for Ibrutinib.**

Samples need to be processed within 1 hour of collection.

SAMPLE HANDLING AND SHIPMENT:

Plasma samples will be shipped to Frontage Lab on dry ice. Please complete **Appendix 2 Plasma Requisition Form** for each participant's specimen and include with the shipment. Specimens should be carefully packaged with suitable packing material to ensure they do not break. Pre-printed shipping labels will be provided by MSK.

All plasma samples and the associated requisition form will be shipped to Frontage Laboratory for analysis. Samples should be shipped on dry ice on **Monday through Wednesday** to the following address:

FRONTAGE LABORATORIES, INC.,

ATTENTION: **JESSICA SCOTT/ MAULIKA PATEL/JOSEPH FALCONE**

SAMPLE COORDINATOR

700 PENNSYLVANIA DRIVE EXTON, PA 19341

PHONE: 484-348-4790 & 484-348-4799

FAX: 610-232-0101

Pharmacokinetic specimens to be batch shipped (frozen) for each subject, please include:

- One primary set of samples for each subject
- One back-up set of samples for each subject (in a separate shipment unless only single plasma sample available)

The following can be found in the **Appendix 1- Plasma Collection manual for Ibrutinib** (Please refer to the manual for further details)

- As much as possible, a complete set of **primary** samples (all time points) for a subject should be batched and shipped together in the same shipment.
- Ship the **back-up** set after the confirmation of receipt of the primary set by Frontage Labs.
- Do NOT ship back-up aliquots of plasma in the same shipment as the primary samples from the same subject.
- To avoid sample mix-ups or misidentification, place the samples in the shipment by subject number and sample time using zip-lock bags or segmented cartons.
- There should be **adequate amount of dry ice** included in the shipment **to last for three days of shipping**.

NOTIFICATION AND PERSONNEL:

Prior to the day that specimen are shipped, please notify by e-mail the MSK PI, study team and Frontage Laboratories.

Site/ Name	Email:	Telephone
MSK PI- Dr. Anita Kumar	Kumara2@mskcc.org	**646-888-4184**
Research Study Assistant: Gianna McArthur	Mcarthug@mskcc.org	**646-888-1004**
Frontage Labs: Mira Hong (Sr. Director, Project Management, Frontage Labs)	Mhong@frontagelab.com	
Frontage Labs: Jessica Scott, Maulika Patel and Joseph Falcone	samplemanagement@frontagelab.com	
Research Study Assistant: Veenna Minnal	minnalv@mskcc.org	**646-449-1316**

In the e-mail notification, please include the following information:

- Study number: **MSK Study # 14-227**
- MSK assigned subject ID
- Date of shipment
- Number of pharmacokinetic samples
- Time of shipment drop-off

- Shipment tracking number
- Copy of **Appendix 2 Plasma Requisition Form**

Peripheral Blood Mononuclear Cell (PBMC)

SAMPLE COLLECTION TIME POINTS:

- **Collection of PBMC from patient blood samples for occupancy assays:** Cycle 1 day 1 predose and 4 hours post-dose; cycle 1 day 8 predose, 1 hour, 2 hours, and 4 hours post-dose; and cycle 2 day 1 (predose)
- Samples will be collected using BD Vacutainer CPT Cell Preparation Tubes with Sodium Citrate for **each patient**.

SAMPLE HANDLING AND SHIPMENT:

Specimens should be kept at ambient temperature (15-30°C) from the time of collection and shipped at ambient temperature on the same day as collection. Please complete **Appendix 3 Peripheral Blood Mononuclear Cell Requisition Form** for each participant's specimen and include with shipment. Specimens should be shipped to MSK in suitable packing material to ensure they do not break. Pre-printed shipping labels will be provided by MSK. Samples shipped same day to MSK **(Monday – Thursday)**

MEMORIAL SLOAN KETTERING CANCER CENTER

408 EAST 69TH STREET NEW YORK NY 10065

(ATTENTION: **Amber Turner)**

STUDY PROTOCOL # 14-227

NOTIFICATION AND PERSONNEL:

Prior to the day that specimen are shipped, please notify by e-mail the MSK PI, and study team

SITE/ NAME:	EMAIL:	TELEPHONE:

MSK PI- Dr. Anita Kumar	Kumara2@mskcc.org	**646-888-4184**
Research Study Assistant: Gianna McArthur	Mcarthug@mskcc.org	**646-888-1004**
Hematologic Oncology Tissue Bank: Amber Turner	turnera1@mskcc.org	**646-888-2210**
Research Study Assistant: Veenna Minnal	minnalv@mskcc.org	**646-449-1316**

In the e-mail notification, please include the following information:

- Study number: **MSK Study # 14-227**
- MSK assigned subject ID
- Date of shipment
- Number of pharmacokinetic samples
- Time of shipment drop-off
- Shipment tracking number
- Copy of **Appendix 3 Peripheral Blood Mononuclear Requisition Form**

SERUM:

SAMPLE COLLECTION and TIME POINTS:

1. **Blood Samples for Serum:** Cycle day 1 (predose) and cycle 2 day 1.
2. Samples will be collected using 10mL red top sodium heparin tube

SAMPLE HANDLING AND SHIPMENT:
Specimens should be kept at ambient temperature (15-30°C) from the time of collection and shipped at ambient temperature on the same day as collection. Please complete **Appendix 4 Serum Requisition Form** for each participant's specimen and include with shipment. Specimens should be shipped to MSK and should be carefully packaged in suitable packing material to ensure they do not break. Pre-printed shipping labels will be provided by MSK. Samples shipped same day to MSK **(Monday – Thursday)**

MEMORIAL SLOAN KETTERING CANCER CENTER

408 EAST 69TH STREET NEW YORK NY 10065

(ATTENTION: **Amber Turner)**

STUDY PROTOCOL # 14-227

NOTIFICATION AND PERSONNEL:

Prior to the day that specimen are shipped, please notify by e-mail the MSK PI, and study team.

SITE/ NAME:	EMAIL:	TELEPHONE:
MSK PI- Dr. Anita Kumar	Kumara2@mskcc.org	**646-888-4184**
Research Study Assistant: Gianna McArthur	Mcarthug@mskcc.org	**646-888-1004**
Hematologic Oncology Tissue Bank: Amber Turner	turnera1@mskcc.org	**646-888-2210**
Research Study Assistant: Veenna Minnal	minnalv@mskcc.org	**646-449-1308**

In the e-mail notification, please include the following information:

- Study number: **MSK Study # 14-227**
- MSK assigned subject ID
- Date of shipment
- Number of samples
- Time of shipment drop-off
- Shipment tracking number
- Copy of **Appendix 4 Serum Requisition Form**

FFPE/ TISSUE BLOCK _SKIN PUNCH BIOPSIES

SAMPLE COLLECTION TIME POINTS:
Skin biopsy will be collected: Cycle 1: Day 1 and day 8

PROCESSING:
Please process FFPE slides or tissue block per standard clinical pathology guidelines.

Required Tissues:

- For patients with CTCL, baseline and post-treatment day 8 biopsy (skin punch biopsies in mycosis fungoides (MF) patients or peripheral blood in Sezary patients) will be mandatory or archival tissue block or 10- 20 unstained slides. (Each slide should contain a sample 10 microns thick cut from the same block.)

- For PTCL patients with cutaneous lesion(s), baseline and post-treatment day 8 biopsies (skin punch biopsy) will be mandatory.

Optional Tissue:

- For PTCL patients with bone marrow involvement, if informed consent is provided by the patient, baseline and post-treatment day 8 bone marrow biopsy may be performed.

Note: For PTCL patients with other sites of involvement (i.e. lymph node or organ), no biopsies will be performed while on ibrutinib therapy due to increased risk of bleeding associated with needle or excisional biopsies. Investigators and patients should make every effort to obtain post-treatment biopsy on day 8; however it is acceptable if tumor biopsy is obtained between days 3-28 if extenuating circumstances arise.

SAMPLE HANDLING AND SHIPMENT:
Samples can be shipped at conclusion of enrollment. Please ship to MSK at ambient temperature to the following address:

MEMORIAL SLOAN KETTERING CANCER CENTER

408 EAST 69TH STREET NEW YORK NY 10065

(ATTENTION: **Amber Turner)**

STUDY PROTOCOL # 14-227

NOTIFICATION AND PERSONNEL:

Prior to the day that specimen are shipped, please notify by e-mail the MSK PI and study team.

- If slides are being shipped, ensure all patient indentifying information is blacked out with a permanent black marker.
- The subject study ID, specimen collection date, and accession number should all be clearly labeled on the slides and the supplemental pathology report.
- Once the tissue sample, requisition and pathology report have been prepared, please package them and send them to MSK.

SITE/ NAME:	EMAIL:	TELEPHONE:
MSK PI- Dr. Anita Kumar	Kumara2@mskcc.org	**646-888-4184**
Research Study Assistant: Gianna McArthur	Mcarthug@mskcc.org	**646-888-1004**
Hematologic Oncology Tissue Bank: Amber Turner	turnera1@mskcc.org	**646-888-2210**
Research Study Assistant: Veenna Minnal	minnalv@mskcc.org	**646-888-2210**

In the e-mail notification, please include the following information:

- Study number: **MSK Study # 14-227**
- MSK assigned subject ID
- Date of shipment
- Specimen collection date
- Time of shipment pick up
- Shipment tracking number
- Copy of **Appendix 5 Skin Punch Biopsy Requisition Form**

TISSUE BANKING (Optional)

We will plan to bank any baseline / pre-treatment tissue specimens from this study for future research to identify biomarkers for response to ibrutinib. It is optional for OSU to send to MSK baseline / pre-treatment tissue specimens.

SAMPLE COLLECTION TIME POINTS: At baseline (pre-treatment).

PROCESSING:
Please process FFPE slides or tissue block per standard clinical pathology guidelines.

SAMPLE HANDLING AND SHIPMENT:

Samples can be shipped at conclusion of enrollment. Please ship to MSK at ambient temperature to the following address:

MEMORIAL SLOAN KETTERING CANCER CENTER

408 EAST 69TH STREET NEW YORK NY 10065

(ATTENTION: **Amber Turner)**

STUDY PROTOCOL # 14-227

NOTIFICATION AND PERSONNEL:

Prior to the day that specimen are shipped, please notify by e-mail the MSK PI and study team.

- If slides are being shipped, ensure all patient indentifying information is blacked out with a permanent black marker.
- The subject study ID, specimen collection date, and accession number should all be clearly labeled on the slides and the supplemental pathology report.
- Once the tissue sample, requisition and pathology report have been prepared, please package them and send them to MSK.

	EMAIL:	TELEPHONE:

SITE/ NAME:		
MSK PI- Dr. Anita Kumar	Kumara2@mskcc.org	646-888-4184
Research Study Assistant: Gianna McArthur	Mcarthug@mskcc.org	646-888-1004
Hematologic Oncology Tissue Bank: Amber Turner	turnera1@mskcc.org	646-888-2210
Research Study Assistant: Veenna Minnal	minnalv@mskcc.org	646-449-1316

In the e-mail notification, please include the following information:

- Study number: **MSK Study # 14-227**
- MSK assigned subject ID
- Date of shipment
- Specimen collection date
- Time of shipment drop-off
- Shipment tracking number
- Copy of **Appendix 6 Tissue Collection Requisition Form**

APPENDICES

APPENDIX 1: PHARMACOKINETIC COLLECTION MANUAL FOR IBRUTINIB

Collect the ibrutinib PK blood samples according to the time points described in the protocol.

USE 1 x 2-mL **GREEN TOP SODIUM HEPARIN TUBE** FOR EACH PK COLLECTION.

1. Allow tube to fill COMPLETELY, as far as the vacuum will allow.
2. Mix the tube immediately upon completion to avoid clotting by inverting gently 5 times. DO NOT SHAKE.
3. Place the blood samples on melting ice until centrifugation
4. Place the sample in a refrigerated centrifuge (0-4°C).

NOTE: Use a refrigerated centrifuge bucket in cases where a refrigerated centrifuge is not available. Maintain cold temperature during the plasma preparation process.

5. Centrifuge tube within 60 minutes of collection at 4°C for 15 minutes at 2500 rpm.
6. Transfer plasma with pipette equally into two 2-mL cryovials (approximately 0.5 mL of plasma in each tube).
7. Enter the Subject ID number on the sample labels.
8. Store plasma samples in a freezer at -70°C or below, within approximately 60 minutes of blood collection.
9. Ship samples **FROZEN** in batches (after collection from each subject is completed) to **Frontage Laboratories.**

NOTE: Every effort should be made to collect the full 2 mL blood sample at each time point. In the event that less than 1 mL of blood is collected, the sample will be processed as described above except that the plasma will not be divided into two tubes. All deviations will be recorded on the PK worksheet. This single plasma sample should be frozen, stored and shipped with the primary set of samples.

All PK Timepoints

TEST	COLLECT	PREPARE	CONTAINER	SHIP TEMP
PK	1 x 2ml Green Sodium Heparin 	Centrifuge & Transfer Plasma	2 x 2ml cryovials 	Frozen to

PK Sample Shipping Instructions from Clinical Sites to Frontage

PK SPECIMENS to be batch shipped (FROZEN) from each subject. Please include:

- One primary set of samples for each subject
- One back-up set of samples for each subject (in a separate shipment unless only single plasma sample available)

Samples should be shipped on dry ice **Monday through Wednesday** only.

As much as possible, a complete set of **primary** samples (all time points) for a subject should be batched and shipped together in the same shipment.

Ship the **back-up** set after the confirmation of receipt of the primary set by Frontage Labs.

Do NOT ship back-up aliquots of plasma in the same shipment as the primary samples from the same subject.

To avoid sample mix-ups or misidentification, place the samples in the shipment by subject number and sample time using zip-lock bags or segmented cartons. There should be **adequate amount of dry ice** included in the shipment **to last for three days of shipping**. Please ship the samples to the following address:

Contact FEDEX customer service to determine the latest pickup time for your site and the scheduling deadline. Record the FEDEX Tracking number from the top of each airbill for your records and tracking purposes.

Notify Frontage Laboratories at least 1 day prior to the arrival of the sample, providing shipping details and tracking numbers for the shipment. The site will e-mail Mira Hong (Sr. Director, Project Management, Frontage Labs) at mhong@frontagelab.com and Jessica Scott, Maulika Patel and Joseph Falcone at samplemanagement@frontagelab.com. The e-mail must specify the study number, the number of pharmacokinetic samples, and the time of shipment pick-up and include an electronic sample inventory.

Prior to shipment, prepare a sample shipment list (or Inventory list) containing the details of each sample / label identification included in the shipment. All of the sample details on this list must correspond with the details included on the individual sample labels, as each sample label will be checked against the list by Frontage sample coordination personnel. Any discrepancies between information on the sample tubes and information on the e-rosters will be verified and noted in the e-rosters prior to shipping. All sample correspondence must contain the Study Number, Study Drug, and Site references (including emergency contact details and responsible shipment coordinator).

SHIPPING ADDRESS

Frontage Laboratories, Inc.,

ATTENTION: **Jessica Scott/ Maulika Patel/Joseph Falcone**

Sample Coordinator

700 Pennsylvania Drive

Exton, PA 19341

Phone: 484-348-4790 & 484-348-4799

Fax: 610-232-0101