TITLE: A Phase I/II Study of Ibrutinib in Previously Treated EGFR Mutant Non-Small Cell Lung Cancer

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1. OBJECTIVES

1.1 Primary Objectives

The primary objectives are to determine the maximum tolerated dose/maximum planned dose of ibrutinib in patients with non-small cell lung cancer and to assess the response rate with ibrutinib in patients with non-small cell lung cancer harboring EGFR mutations with progression on EGFR TKIs.

1.2 Secondary Objectives

Secondary objectives are to assess:

- Response rate in patients with HER2 mutant non-small cell lung cancer
- Disease control rate (defined as rate of stable disease + partial response + complete response)
- Overall survival
- Progression-free survival
- Safety and toxicity profile
- Duration of response.

Exploratory objectives are:

- To assess molecular markers associated with resistance and response, including secondary mutations.
- To perform pharmacokinetic studies

2. BACKGROUND

2.1 EGFR Mutant and HER2 Mutant Non-Small Cell Lung Cancer

Activating mutations in the epidermal growth factor receptor (EGFR) are found in approximately 10 to 15% of patients with non-small cell lung cancer (NSCLC).[1,2] For these patients, treatment with EGFR tyrosine kinase inhibitors erlotinib, afatinib, or gefitinib (TKIs) is associated with high response rates and improved progression free and overall survival.[3,4] Unfortunately, acquired resistance inevitably develops, occurring at a median of 10 to 13 months after treatment initiation. A variety of resistance mechanisms have been identified, including the secondary EGFR mutation, T790M.[5-7] Attempts to target this resistant population have been relatively unsuccessful to date, with the irreversible EGFR inhibitor afatinib showing no survival benefit compared to placebo in patients who have failed therapy with erlotinib or gefitinib.[8]
Other major limitations of the approved EGFR TKIs currently are their toxicities, particularly GI and skin effects, which are due to inhibition of wild-type EGFR.[9-11] There is therefore an urgent unmet need for new agents that inhibit the mutated EGFR tyrosine kinase, including those with resistance mutations such as T790M, while minimizing toxicities related to inhibition of the wild-type EGFR receptor.

HER2 mutations have been described in about 1 – 2% of patients with NSCLC. There are no approved targeted therapies for patients with these mutations.

2.2 Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA ™) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, 3) CLL in patients with 17p deletion and 4) Waldenström's Macroglobulinemia. Ibrutinib is currently under investigation in various indications.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways.[12]

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development.[13] Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells.[14]

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure.

2.2.1 Summary of Nonclinical Data

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

2.2.2 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk.[15] In vitro, ibrutinib is a potent inhibitor of Btk activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[16]

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current Investigator's Brochure.

2.2.3 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

2.2.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

2.2.4 Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

In a phase II study in patients with mantle cell lymphoma, 111 patients received oral ibrutinib at a dose of 560 mg daily. All patients had received at least one prior chemotherapeutic regimen, with a median of three prior regimens. Treatment was well tolerated – the most common adverse events were low grade diarrhea, nausea, and fatigue. The most common grade 3/4 adverse events were neutropenia and thrombocytopenia in 16% and 11% of patients, respectively. The response rate to therapy was 68%, with 21% of patients having a complete response. The median progression free survival on this study was 13.9 months; median overall survival has not yet been reached.[17]

In a phase Ib/II study enrolling patients with relapsed or refractory chronic lymphocytic leukemia, 85 patients received oral ibrutinib at doses of 420 mg once daily or 840 mg once daily. Again, treatment was well tolerated, and the most common adverse events were diarrhea, upper respiratory tract infection, and fatigue. Most of these were low grade. The most common grade 3/4 adverse event was neutropenia, which occurred in 15% of patients. No other grade 3/4 event occurred in more than 5% of patients. The overall response rate was 71% and was not significantly different between the low dose and high dose groups. At 26 months, estimated progression free survival was 75% and overall survival was 83%.[18]

2.2.5 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively

metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

2.3 Rationale

Ibrutinib is efficacious and well tolerated in certain lymphomas and leukemias, but its activity in solid tumors has not yet been extensively studied. To test whether ibrutinib might have utility in the treatment of lung cancer, we evaluated its antitumor activities in a panel of lung cancer cell lines by using a cell viability assay 3 days after treatment with 0.01 to 31 uM ibrutinib. For the 39 NSCLC cell lines tested, the 50% inhibitory concentration (IC_{50}) of ibrutinib ranged from 0.002 to 31 μM, with an average of 12.4 μM. Three NSCLC cell lines were highly susceptible to ibrutinib, with IC50s between 0.002 and 0.195 μM. Two of these cell lines harbor activating EGFR mutations; the third, though EGFR wild type, expresses constitutively active EGFR and is sensitive to erlotinib as well.

We next compared erlotinib and ibrutinib antitumor activities in nine NSCLC cell lines, six of which have mutations or deletions in the EGFR gene. Five of six EGFR mutant cell lines were susceptible to both erlotinib and ibrutinib, with IC50s < 0.2 μM. The H1975 cell line, which harbors a T790M mutation in EGFR, was resistant to erlotinib but susceptible to ibrutinib. The expression of BTK was not detectable in all cell lines tested, indicating that ibrutinib-induced antitumor activity in these cells is not mediated by BTK. We then analyzed the effects of ibrutinib on EGFR phosphorylation. Treatment of H1975 and H3255 cells with erlotinib and ibrutinib led to a similar dose-dependent inhibition of phosphor-EGFR at the Y1068 site in H3255 cells. However, only ibrutinib inhibited pY1068 in H1975 cells which harbor the T790M mutation. Similar results were observed in other cell lines. Those results suggested that ibrutinib can function as an EGFR inhibitor in NSCLC cells, even though it does not have a 4-anilinoquinazolin core structure as most other EGFR inhibitors.

We also tested in vivo activity of ibrutinib in a xenograft tumor model derived from H1975 cells. The results showed that treatment with 25 mg/kg of ibrutinib significantly suppressed H1975 tumor growth and prolonged survival of tumor bearing animals when compared with vehicle treated animals. In contrast, treatment with 50mg/kg of erlotinib had no effect on both tumor growth and survival in the same model, demonstrating in vivo efficacy of ibrutinib in EGFR

mutant and erlotinib resistant NSCLC cancer.

We also saw evidence of ibrutinib activity in NSCLC cell lines carrying an activation HER2 mutation.

Based on pre-clinical data suggesting inhibition of growth in EGFR mutant NSCLC cell lines, including those with the T790M resistance mutation, we propose this phase II trial to determine the activity of ibrutinib in patients with NSCLC harboring activating EGFR mutations whose tumors have progressed on therapy with erlotinib or gefitinib. Based on our preclinical data suggesting activity in HER2 mutant cell lines, we will also assess the activity of ibrutinib in patients with HER2 mutant NSCLC.

2.4 Correlative Studies Background

All patients with EGFR mutations will be required to have tissue acquired after resistance to an EGFR targeted tyrosine kinase inhibitor (e.g. erlotinib, gefitinib, or afatinib). We will analyze this tissue for resistance mechanisms to EGFR inhibitors, such as secondary mutations in T790M, amplification of MET, and epithelial-to-mesenchymal transition (EMT).[7] Patients with HER2 mutant NSCLC will be required to have tissue availability following progression on their most recent line of therapy, either targeted therapy or chemotherapy. For both groups, if no tissue is available, a biopsy will be arranged prior to treatment on study for these analyses.

Patients will have the option to have blood drawn for blood-based biomarkers, including profiling of plasma cytokine and angiogenic factors and circulating free plasma DNA, as described in section 8.1.2.

Pharmacokinetic analyses will also be performed as described in section 8.2.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed stage IV non-small cell lung cancer, or recurrent non-small cell lung cancer which is not amenable to curative intent therapy.

3.1.2 Patients must have measurable disease by RECIST 1.1 criteria

3.1.3 For EGFR mutant cohort, patients must have:

- Documented EGFR mutation by CLIA-certified test
- Documented disease progression on treatment with erlotinib, gefitinib, afatinib, or other EGFR-targeted tyrosine kinase inhibitor
- Tissue available from a biopsy or surgical procedure performed after progression on an EGFR targeted tyrosine kinase inhibitor. If tissue is not available, the patient must have biopsy accessible disease and must be willing to undergo a biopsy.

3.1.4 For HER2 mutant cohort, patients must have:

- Documented HER2 mutation by CLIA-certified test
- Documented disease progression on treatment with erlotinib, gefitinib, afatinib, or other EGFR-targeted tyrosine kinase inhibitor
- Tissue available following progression on most recent systemic therapy. If tissue is not available, the patient must have biopsy accessible disease and must be willing to undergo a biopsy.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status ≤2

3.1.7 Ability to take pills by mouth

3.1.8 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥9 g/dL
– total bilirubin	≤1.5 x institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤2.5 × ULN or ≤5 x ULN if metastases to the liver
– creatinine clearance	≥45 mL/min

3.1.9 Patients with asymptomatic brain metastases are allowed, as long as they are stable and do not require treatment with anticonvulsants or escalating doses of steroids. Maximum daily dose of steroids should be prednisone 20 mg or equivalent. Radiation therapy for brain metastases must be completed at least 14 days prior to treatment on protocol.

3.1.10 The effects of ibrutinib on the developing human fetus are unknown. Women of child-bearing potential and men must agree to use highly effective contraception (if using hormonal birth control must add a second barrier method; abstinence) prior to study entry, for the duration of study participation as well as for at least 1 month after the last dose of ibrutinib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use highly effective contraception prior to the study, for the duration of study participation and 3 months after completion of ibrutinub administration.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have received EGFR tyrosine kinase inhibitors within 72 hours of initiation of study treatment, or treatment with other anti-cancer agents within 21 days of study treatment

3.2.2 Prior treatment with ibrutinib

3.2.3 Known hypersensitivity to ibrutinib

3.2.4 Concurrent use of agents that strongly inhibit or induce CYP3A unless use is approved by the medical monitor (see section 4.4.2.1 for details regarding specific agents).

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant and nursing women.

3.2.7 Patients with a history of another active malignancy within the past two years, with the exception of non-melanoma cutaneous malignancy, cervical carcinoma in situ, or ductal carcinoma in situ which has been successfully treated with curative intent therapy.

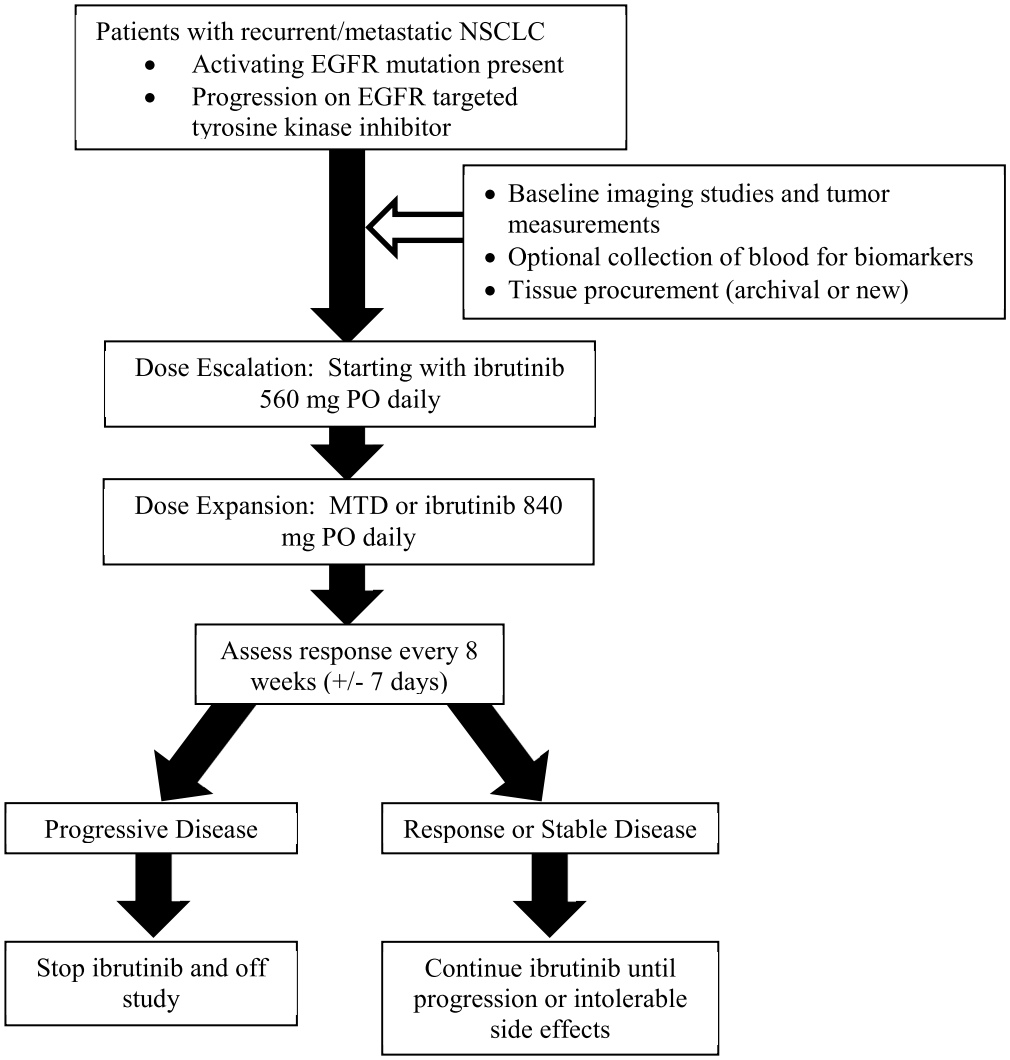
3.2.8 Any gastrointestinal disorder expected to limit absorption of ibrutinib

3.2.9 Treatment with warfarin or other vitamin K antagonist. Patients with using warfarin who switch to another form of anticoagulation will be eligible.

3.2.10 Patients with persistent and uncontrolled atrial fibrillation.

4. TREATMENT PLAN

4.1 Study Schema



4.2 Dose Escalation and Agent Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose escalation will proceed by the following plan:

Dose Level	Ibrutinib Dose
-2	280 mg PO daily
-1	420 mg PO daily
0-Starting Dose	560 mg PO daily
1	840 mg PO daily

Dose limiting toxicity (DLT) is defined in Section **4.3** and will be evaluated after the completion of Cycle 1. Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 0. New cohorts of patients will not be treated until toxicity has been evaluated for all current patients. The algorithm is as follows: (1) If 0 out of 3 patients experiences DLT, the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develops DLT, additional 3 patients will be treated at the same dose level. If no more DLT develops at the dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues to next higher level for a cohort of 3 patients. (3) At any given dose, if more than 1 out of 3 patients or 6 patients experience DLT, the dose level exceeds the MTD and 3 patients will be treated at the next lower dose level if there are less than 6 patients already treated at that dose. If this is the lowest dose level tested, the trial will be terminated and MTD is not found. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with at most 1 instance of DLT. Given these dose levels and 6 patients treated at MTD, it is anticipated that up to 24 eligible patients are required for the dose escalation part of the study.

The principal investigator will evaluate each individual cohort within a dose level and make a recommendation regarding dose escalation or de-escalation. If there are 2 DLTs in Dose Level 0, Dose Level -1 will be enrolled. If there are 2 DLTs in Dose Level -1, Dose Level -2 will be enrolled. If there are 2 DLTs in Dose Level -2, the enrollment will be stopped for the study. The MTD will be defined as the highest dose at which $\leq$1 of 6 of patients in the cohort experiences a study treatment related DLT. The maximum planned dose is 840 mg PO daily; if this dose is well tolerated, it will be used for the remainder of the study.

Before applying the dose escalation rules, all patients in one cohort must have been evaluated for toxicity.

Once the MTD has been determined, the MTD cohort will be expanded up to a total of 20 EGFR mutant patients, including the patients enrolled for dose escalation, and 5 HER2 mutant patients following the Gehan's 2-stage Design.
The maximum accrual of the study will be 43 patients.

The study drug will be administered on a continuous basis on 28 day cycles. Patients will be instructed to take the study medication at the same time every day.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

Expired and used medications will be destroyed per MD Anderson institutional policy.

4.3 Definition of Dose-Limiting Toxicity (DLT)

Toxicities will be described according to NCI-CTCAE version 4.0. Dose-limiting toxicity is defined as toxicity that is possibly, probably, or definitely attributable to the study regimen in the opinion of the principal investigator and that is:

- Grade 3 or higher non-hematologic toxicity excluding nausea and vomiting and skin rash

- Grade 4 neutropenia, febrile neutropenia, or grade 4 thrombocytopenia
- Grade 3 or higher nausea and vomiting that cannot be controlled within two weeks with anti-emetics
- Grade 4 skin rash

As an exception, if the toxicity is regarding as being possibly related to the study regimen but in the opinion of the principal investigator is felt to be more likely related to a concurrent medication, the underlying malignancy, a co-morbid condition, or some factor other than the study regimen, the principal investigator may choose to not regard it as a DLT for the purposes of the study.

Any DLT that occurs within the first cycle of therapy (28 days) will be used to make decisions about proceeding to the subsequent cohort.

4.4 General Concomitant Medications, Procedures, and Supportive Care Guidelines

4.4.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines.[19] Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

4.4.2 Medications to be Used with Caution

4.4.2.1 CYP3A- Inhibitors/Inducers

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 (eg, ketoconazole, indinavir, nelfinavir, ritonavir,

saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) 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.

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 (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

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.

4.4.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

4.4.2.3 QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

4.4.2.4 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 with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.2).

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib/ placebo held, the sponsor's medical monitor should be

contacted, and ibrutinib/placebo should not be restarted until the subject is clinically stable and the re-initiation of ibrutinib/placebo is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

4.4.3 Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

Erythropoietic growth factors (eg, erythropoietin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) are also prohibited during the first cycle of therapy while DLTs are being assessed.

4.4.4 Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. 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.

4.4.4.1 Emergency 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.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient non-compliance,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Patients will be followed for 6 months after removal from study or until death, whichever occurs first. Subjects removed from treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event(s). These patients will then, subsequently be followed for long term survival every 6 months.

4.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.5 applies or patient is lost to follow up. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5. DOSING DELAYS/DOSE MODIFICATIONS

Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological toxicities, grade 3 or greater neutropenia with infection or fever, or grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib may be re-initiated at the starting dose. If the toxicity reoccurs, reduce the dose as described in the table below. If these toxicities persist or recur following two dose reductions, ibrutinib will be permanently discontinued.

Recommended dose modifications for these toxicities are described below:

Toxicity Occurrence	Starting Dose: 840 mg	Starting Dose: 560 mg	Starting Dose: 420 mg
First	Restart at 840 mg daily	Restart at 560 mg daily	Restart at 420 mg daily
Second	560 mg daily	420 mg daily	280 mg daily
Third	420 mg daily	280 mg daily	140 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib	Discontinue ibrutinib

Dose reductions are permanent once implemented.

6. ADVERSE EVENTS AND REPORTING

ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

Definitions

Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- 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 that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v4.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in patient death

Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All Grade 3 – 5 adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

Serious Adverse Event Reporting (SAE) Reporting

Important medical events may also be considered serious adverse events.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

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.

Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per the SAE reporting timelines.

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.

Events meeting the definition of major hemorrhage will be captured as an event of special interest.

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.

Communication between Investigator and Pharmacyclics

All serious adverse events and AESIs (initial and follow-up information) will be reported on MD Anderson SAE form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

7. IBRUTINIB OVERALL SAFETY SUMMARY

7.1 Monotherapy Studies

The integrated safety profile of ibrutinib administered as monotherapy to 506 subjects across 8 company-sponsored 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 (reference: Investigator's Brochure Version 7, dated 31 July 2013). 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 higher 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 or higher 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%).

In addition, data is available from combination therapy clinical studies. Refer to the latest version of the IB for more details.

7.2 Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each).

7.2.1 Hemorrhagic 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. And none were reported in any healthy volunteer studies (n=100).

Due to multiple confounding factors (such as older age, advanced stage cancer, comorbidities, and concomitant medication usage), it is unclear whether or not these hemorrhagic events were attributable to ibrutinib.

7.2.2 Cardiac

Atrial fibrillation and atrial flutter have been reported in patients 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.

7.2.3 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.

7.2.4 Other Malignancies

Other malignant diseases have been observed in subjects who have been treated with ibrutinib, including skin cancers, other carcinomas, and other hematologic malignancies. It is not clear whether or not these events are attributable to ibrutinib. Subjects in the current study will be monitored for other malignancies.

7.2.5 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.

8. CORRELATIVE, BIOMARKER, AND PHARMACOKINETIC STUDIES

To better understand the activity of ibrutinib, and to try to determine which patients may benefit from this therapy, we plan a number of correlative studies.

8.1 Biomarker Studies

Biomarker samples will be stored at MD Anderson for no longer than 15 years.

8.1.1 <u>Exploration of mechanisms of resistance to EGFR inhibitors</u>

All patients with EGFR mutations will have tumor tissue available from after progression on an EGFR targeted tyrosine kinase inhibitor. We will also request archived tissue from prior biopsies if available. Depending on the availability and quality of tissue, we plan to perform a number of studies to explore resistance mechanisms to EGFR targeted therapies. Specifically, we will perform comprehensive molecular profiling, which will include genetic analysis of the *EGFR* gene for primary and secondary mutations as well as such testing for amplification of MET and activation of Axl. We will also evaluate markers of the epithelial-to-mesenchymal transition using immunohistochemical staining for E-cadherin and vimentin, in addition to other markers.

An optional tumor tissue biopsy will be collected at the end of treatment for exploratory biomarker analysis from consented patients.

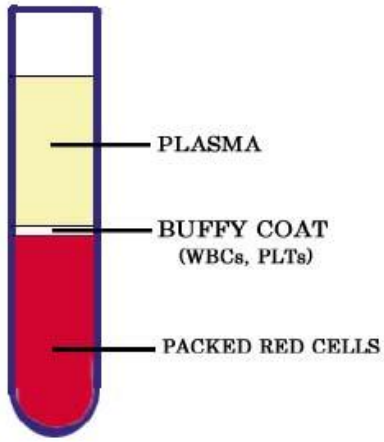
8.1.2 Blood-based Biomarkers

For patients who consented for optional blood-based biomarker studies, blood will be collected as outlined below. Plasma cytokine and angiogenic factors (CAF) profiling, circulating free plasma DNA and T cell subsets and cytokines (TH1/TH2) will be analyzed to evaluate for potential markers of clinical benefit to treatment and molecular alterations; respectively.

Blood-based Biomarkers – Blood Collection, Processing and Storage

1. Total volume to be collected: 44 mL
2. Blood will be collected at the following time points: baseline (pre-treatment, end of Cycle 2, and end of study)

- For CAF profiling and circulating free plasma DNA
  1) Collect whole blood in three (3) x 8 mL "EDTA" K2EDTA Vacutainer, BD Diagnostics, Franklin, NJ, USA)
  2) Preparation of **Plasma:**
     a. Label three (9) 2 mL cryovials with the study number, case number, and procedure date, and clearly mark cryovials "plasma."
     b. Process: place EDTA tube in a standard clinical centrifuge and set at ~2500 RPM at 4° Celsius for 10 minutes.
     c. **Centrifuge within 30 minutes of collection.** If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
     d. Aliquot 1.5 mL of plasma into each cryovials labeled with the study and case numbers and procedure date and marked "plasma."
     e. Place cryovials into cryobox with appropriate study labeling
     f. Store at a minimum –70 Celsius until ready for shipment or analysis.
  3) Preparation of Buffy coat:
     For a visual explanation of Buffy coat, please refer to diagram below.



a) Label three (3) 1 ml cryovials with the study number, case number, and procedure date, and clearly mark cryovials "buffy coat."
b) Process: Place EDTA tube in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes. **Centrifuge within 30 minutes of collection.**
c) *If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.*
d) Remove plasma close to the buffy coat and keep the plasma for procedure II (*see above instructions for plasma collection*)
e) Remove the buffy coat cells carefully, combine and place into the 2 mL (total of four) cryovials labeled "buffy coat" (*it is acceptable for a few packed red cells inadvertently to be collected in the process*).
f) Place equal volume of cell-storage solution (RPMI/DMSO (70:30))
g) Store buffy coat cryovial at -70 C until analyzed.

- For T cell subsets and cytokines (TH1/TH2)
  1) Collect whole blood in two (2) x 10ML sodium heparin tubes
  2) Isolate plasma and peripheral blood mononuclear cell (PBMC) by a Ficoll processing step.
  3) Store the (undiluted) plasma in cryovials at -80^{o} C.
  4) Viably cryopreverve the PBMC on 10% dimethyl sulfoxide (DMSO)/90% fetal bovine serum (FBS) and store in liquid nitrogen.

8.2 Pharmacokinetic Studies

8.2.1 Collection of Specimens

Blood samples for pharmacokinetic studies will be drawn on Cycle 2, day 1 of treatment at following time-points: predose and at 1, 2, 4, and 6 h post-dose

8.2.2 Handling of Specimens(s)

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: When necessary 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 -80°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, Inc**.

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.

8.2.3 Shipping of Specimen(s)

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

- One primary set of samples for each subject
- One back-up set of samples for each subject (unless only single sample available)

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

As much as possible, a complete set of **primary** samples (all timepoints) 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 Laboratories, Inc.

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

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.

Note: A Shipping Notification fax should be send prior to shipping.
Electronic packaging slip must be sent to naleem@frontagelab.com and mhong@frontagelab.com

SHIPPING ADDRESS
Nabeela Aleem
Sample Coordinator
Frontage Laboratories, Inc.
700 Pennsylvania Drive
Exton, PA 19341
P: 484-348-4790
F: 610-232-0101

9. STUDY PROCEDURES AND CALENDAR

9.1 Informed Consent

Written informed consent will be given by each patient prior to undergoing protocol specific evaluations and prior to receiving treatment.

9.2 Medical History and Physical Exam

A complete medical history and physical exam including vital signs, height, and weight should be obtained within 28 days prior to initiation of therapy on study. ECOG performance status should be recorded at this visit.

9.3 Clinical Laboratory Tests

Blood based clinical laboratory tests will be obtained within 28 days prior to the start of protocol therapy and then every 28 days +/- 7 days. These tests will include:

Hematology profile: complete blood count with differential and platelet count
Chemistry profile: BUN, creatinine, sodium, potassium, carbon dioxide, magnesium, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase
Pregnancy test: Serum or urine pregnancy test will be obtained at baseline within 7 days prior to treatment in all women of child-bearing potential at baseline and again if clinically indicated.

9.4 Tumor Biopsy

If a patient does not have sufficient tissue from a biopsy performed after progression on EGFR-targeted TKI, a biopsy will be performed. The investigator will determine the safest method for obtaining tissue, which could include CT-guided core needle biopsy.

9.5 Radiographic Assessment

Imaging studies including a CT of the chest and other studies as clinically indicated will be performed within 28 days prior to the initiation of study treatment and every 8 weeks (+/- 7 days) while on therapy.

9.6 Study Calendar

Required Procedures	**Baseline**	**During Treatment**	**End of Treatment***	**Long Term Follow-Up**
Timing	Within 28 days prior to treatment initiation unless otherwise specified	Every 4 weeks, ± 7 days, unless otherwise specified	Within 30 days after the last dose of study medication unless otherwise specified	
Treatment History	X			
Medical History	X			
Demographics	X			
Physical Exam	X	X	X	
Vital Signs	X	X	X	
Height	X			
Weight	X	X	X	
ECOG PS	X			
Symptoms & Toxicities	X	X On an ongoing basis throughout study	X	
Concomitant Medications	X	X On an ongoing basis throughout study	X	
Hematology Profile	X	X	X	
Chemistry Profile	X	X	X	
Pregnancy Test (serum or urine) For all women of child bearing potential	X Within 7 days prior to treatment	If/when clinically indicated	If/when clinically indicated	
Radiology & Tumor Measurements	X	X Every 8 weeks, ± 7 days		
Verification of Tissue Availability	X*			
Fresh Biopsy	X**		X***	
Pharmacokinetic studies		#		
Blood-based biomarkers (optional)	X	X[a]	X	
Ibrutinib Compliance		X At each clinic visit		
Subsequent Anticancer Therapy				X
Survival Status				X****

*Tissue from a biopsy or surgical procedure following progression on an EGFR targeted tyrosine kinase inhibitor for EGFR mutants or following most recent line of systemic therapy for HER2 mutants must be available prior to the start of therapy.

**If no tissue obtained following progression on an EGFR TKI for EGFR mutants or most recent systemic therapy for HER2 mutants is available, a biopsy will be performed after signing informed consent but prior to treatment initiation.
***Optional biopsy – within 30 days of last dose of ibrutinib
****Long term follow-up will occur every 6 months by medical/clinical data review or phone contact.
Plasma samples for PK evaluation at steady-state on Day 1, Cycle 2: predose, 1, 2, 4, and 6 h post-dose
[a] CAF profiling and circulating free plasma DNA samples will be collected at the end of Cycle 2. TH1/TH2 samples will be collected every 4 weeks for the first 3 months, then every 12 weeks until the end of treatment.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks +/- 7 days. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[20] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ibrutinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately

measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area can be considered measurable if there has been documented progression in these lesions following the completion of radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted

throughout follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment. In this study, we prefer contrast-enhanced CT scans for imaging of the chest, abdomen, and pelvis, and MRI for imaging of the brain, though other techniques can be used if there is a pressing reason.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) in the opinion of the

collaborating diagnostic radiologist, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers will not be used to assess response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or

scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes* or No	PD	no prior SD, PR or CR
Any	PD**	Yes* or No	PD	
Any	Any	Yes*	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD

Any	Yes	PD
*	'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised	

10.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

10.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.1.7 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to time of progression or death.

11. DATA REPORTING / CAPTURE

The institutional database PDMS/CORE will be used as the electronic case report form for this protocol. Protocol specific data and adverse events will be captured into PDMS/CORE.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a single-institution, single arm phase II study. The primary endpoint of this study is overall response rate using RECIST 1.1 criteria. The response will be evaluated after two cycles of therapy and every 8 weeks thereafter.

Secondary endpoints are disease control rate (defined as the rate of complete response + partial response + stable disease), overall survival, progression-free survival, safety and toxicity and duration of response. Exploratory endpoints include correlation of response with molecular markers including secondary mutations.

12.2 Sample Size/Accrual Rate

Up to 24 patients may be enrolled in the dose escalation portion. Once the MTD has been declared, we plan to accrue 20 evaluable patients with EGFR mutations at MTD. We expect to accrue one to two patients per month. In addition, we plan to enroll 5 patients with HER2 mutant NSCLC at MTD.
The primary endpoint of the study is overall response rate in patients with EGFR mutations using RECIST. The response status will be evaluated after two cycles of treatment and confirmed at least four weeks after. A response rate of 15% or greater would be meaningful in this patient population. When the probability of rejecting a "good" regimen (i.e. response rate>=15%) is 0.10, Gehan's[21] design requires to enter 14 patients with EGFR mutations at the maximum tolerated dose (or maximum planned dose) in the first stage.

Among these 14 patients with EGFR mutations, if no patient responds to the treatment, the trial will be stopped, accrual will be halted, and the regimen will be declared as ineffective. If there are 1 or more responses among the first 14 patients treated at MTD, 6 more patients will be entered in the study to reach a total of 20 patients at the MTD. With 20 patients, the response rate can be estimated with a standard error no larger than 0.112.

Given the small number of patients (five) with HER2 mutant NSCLC that will be enrolling on this protocol, there are no interim stopping rules for efficacy for these patients. These patients will be considered with the rest of the group for toxicity assessment, but efficacy assessment will be calculated separately.

During the expansion cohort, at any time if the DLT rate among patients treated at the MTD dose exceeds 30%, we will stop the accrual at current dose level and enroll the rest of patients into the next lower dose level if the current dose is not dose level -2.

12.3 Analysis of Endpoints

12.3.1 Evaluation of Toxicity

All patients who received ibrutinib will be evaluable for toxicity from the time of their first treatment with ibrutinib.

12.3.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data, such as if a patient drops out early for toxicity before response evaluation). Response will be assessed by RECIST 1.1 criteria.

All of the patients who met the eligibility criteria and received study medication should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). Consideration will be given to replacement of patients who discontinue treatment early for reasons other than progressive disease or toxicity.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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