THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Pilot Study to determine the effects of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using Heavy Water Labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).
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Core Protocol Information

Short Title	Pilot Study to determine effects of the Btk inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using Heavy Water Labeling in subjecfts with CLL and SLL
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Full Title:	A Pilot Study to determine the effects of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using Heavy Water Labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

Protocol PCI-heavy water trial Revised 08-15-14.pdf

A Pilot Study to determine the effects of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using Heavy Water Labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).

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1.0 Introduction

PCI-32765 is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3,4-d]pyrimidin-1-yl]-1piperidinyl]-2-propen-1-one, CAS Registry Number 936563-96-1. PCI-32765 is a first-in-class selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (Btk) currently under investigation in B-cell malignancies. When formulated, the investigational product is PCI-32765, a hard gelatin capsule

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulin's (sIgs) that comprise part of the B-cell antigen receptor (BCR); the sIgs are the antigen-capturing portion of the BCR, and BCR-associated molecules (e.g., CD79a and CD79b) are the units that activate a B cell after 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. The process of B-cell maturation, including Ig chain rearrangement and somatic mutation, is tightly regulated, and it is thought that B-cell lymphomas and CLL result from mutations acquired during normal B-cell development. Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies. First, expression of a functional BCR is maintained throughout lymphoma progression, even when the non-expressed immunoglobulin heavy chain (IGH) is involved in oncogenic translocations and despite prolonged treatment of tumor cells with anti-idiotype therapies. In addition, selective knockdown of BCR components by RNA interference results in apoptosis in multiple B-cell lymphoma cell lines. Recent studies indicate that some large B-cell lymphomas have low level tonic activation of kinases downstream of the BCR and that inhibition of this tonic signaling can induce apoptosis. Primary follicular lymphoma cells have also been found to maintain enhanced signaling from the BCR compared with normal B cells. Finally, at least 2 drugs that target BCR signaling (the Syk inhibitor, R788, and the PKCß inhibitor, enzastaurin) have shown evidence of anti-tumor effects in human B-cell lymphomas.

The role of Btk in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease, X-linked agammaglobulinemia (XLA), and the mouse genetic immunodeficiency disease, X-linked immunodeficiency (xid), 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 (NK) cells, but the selective effect of Btk mutations suggests that its primary functional role is in antigen receptor signaling in B cells. Btk is activated by the upstream Src-family kinases Blk, Lyn and Fyn, and Btk in turn phosphorylates and activates phospholipase-C (PLC), leading to Ca++ mobilization and activation of NFκB and MAP kinase pathways. Given the central role of Btk in BCR signaling and the importance of BCR signaling in lymphoma, inhibition of Btk by PCI-32765 may be an effective therapeutic strategy in B-cell malignancies.

2.0 Background

2.1 Chronic Lymphocytic Leukemia (CLL)

CLL is the most common form of adult leukemia in the United States. It has been estimated that there are approximately 150,000 individuals living with CLL in the United States. The use of chemoimmunotherapy as initial therapy is associated with high response rates, but this therapy is less effective and displays more side effects in elderly subjects. Once disease relapse has occurred after chemoimmunotherapy, second line treatment is less effective and response durations are shorter. An alternative to repeating chemoimmunotherapy is to use the monoclonal antibody (mAb) alemtuzumab. Alemtuzumab can induce a therapeutic response in up to 30% of subjects, but is associated with significant immunosuppression and infections; also, it lacks activity in subjects with bulky lymphadenopathy (larger than 5 centimeters;[1]. Combinations of purine-analogue based regimens have limited activity, and once subjects are fludarabine refractory their median survival is <12 months based on published experience[2].

Kinase inhibitors affecting signaling of the BCR, such as PCI-32765, are an alternative, targeted therapeutic approach for relapsed and elderly CLL subjects, based on promising results in early-phase clinical trials and lack of toxicities. Characteristically, treatment with PCI-32765 induces a rapid reduction in lymphadenopathy, which is accompanied by a transient lymphocytosis; the latter is thought to be due to re-distribution of CLL cells from tissues into the peripheral blood. Then, inhibition of BCR-related survival signaling by PCI-32765 causes "starvation" and a slow-onset, continuous reduction of the leukemia cell burden over time. These mechanisms of action have not been formally demonstrated *in vivo*. Labeling of the DNA of newly-born CLL cells with deuterium (^2H), administered in the form of ^2H_2O prior to therapy with PCI-32765, will allow us to determine the effects of PCI-32765 on leukemia cell mobilization from tissues into the peripheral blood, and on leukemia cell kinetics (proliferation, survival, and cell death).

This trial will address the overarching question how much of the anti-leukemia activity of PCI-32765 is due to re-distribution of CLL cells from the tissues into the blood versus direct effects of PCI-32765 on CLL cell proliferation and cell death by analysis of effects of PCI-32765 on CLL cell tissue redistribution and birth rates. The expected result is that PCI-32765 affects both, tissue redistribution and birth rates of CLL cells, based on pre-clinical work[3] and the more mature clinical data with single-agent PCI-32765[4]. These information are important not only for better understanding of the mechanism of action of PCI-32765, but potentially also for the further development and optimal use of this drug in CLL patients. For example, if PCI-32765 would be found to mainly cause CLL cell redistribution, without effects on birth rates of CLL cells, one could argue that the drug should preferentially be developed in combination with a cytotoxic agent.

2.2 Heavy Water Labeling in subjects with Chronic Lymphocytic Leukemia (CLL).

A fundamental disorder in cancer is altered cell kinetics (imbalance in cell proliferation and/or death). The ideal biomarker for cancer would therefore measure these cellular kinetic events directly. CLL is an excellent clinical cancer model for applying a kinetic biomarker, by virtue of its accessibility (being a liquid tumor) and its relatively well-established kinetic basis. The laboratory of Dr. Marc Hellerstein at the University of

California has developed, patented, and extensively used a direct kinetic biomarker of cell proliferation and death in humans. The technique is based on stable (non-radioactive) isotope incorporation (e.g., deuterium, ^{2}H) into cellular DNA at the time of cell division followed by gas chromatography/mass spectrometry (GC/MS) analysis of deuterated deoxyadenosine. This technology is exclusively licensed to KineMed, Inc., a company formed to commercialize kinetic measurements in medical diagnostics and drug development. Previously our understanding of the kinetics of cells *in vivo* was limited. Indeed, most contemporary data that characterize the proliferation rates of cells are derived from *ex vivo*, static measurements using toxic labels, such as ^{3}H-thymidine or bromodeoxyuridine (radioactive and mutagenic, respectively;[5,6]. These approaches are limited not only by inherent toxicity, but also because they have low reproducibility, are non-quantitative, and suffer from other technical limitations. Most importantly, these techniques cannot be used safely in humans *in vivo*. Therefore, the safe and non-toxic $^{2}H_2O$ method for accurately measuring cell proliferation and turnover in CLL *in vivo* could prove to be of significant prognostic utility. After $^{2}H_2O$ is orally ingested, ^{2}H is incorporated into all hydrogen-containing molecules that are being synthesized *in vivo*. For our purposes, the deoxyribose (dR) moiety of purine deoxyribonucleotides in DNA of dividing cells is a valuable marker. Blood or bone marrow is obtained at appropriate time points, during and after the $^{2}H_2O$ consumption/labeling period, CLL cells are isolated, DNA extracted, and the amount of ^{2}H incorporated into deoxyadenosine of DNA is quantified by GC/MS, allowing for a measure of cellular proliferation. ^{2}H is not radioactive, and there are no known major risks of heavy water ingestion at the doses that we will administer [7]. Transient dizziness/vertigo can be experienced in some subjects (~15%). This technique has been used to measure cellular proliferation in both humans and animals. Some examples in humans follow.

2.3 Cell Division Studies in Humans Using Heavy Water Labeling

The heavy water method has been applied to measure the kinetics of human T cells in normal and HIV infected individuals, showing a significantly increased T-cell turnover rate in untreated HIV^{+} subjects that improves with treatment (5). This technique has also been used to assess breast epithelial cell proliferation in women from samples taken with a core needle biopsy; it was found that pre-menopausal woman had a significantly increased cell turnover compared to postmenopausal women.

Dynamic Proteomics

KineMed has developed a new technological platform based on quantitation of turnover rates of multiple proteins simultaneously[8]. This powerful "dynamic proteomics" technique can be used in living animals and humans[8-10] (Figure. 3). The kinetics of hundreds of proteins are measured concurrently, using stable isotope labeling (e.g., with heavy water) *in vivo* followed by analysis of trypsin-derived peptides by liquid chromatographytandemmass spectrometry (LC/MS-MS). The perturbation in mass isotopomer patterns in peptides reveals the synthesis and/or removal rates of their parent proteins [9,10]. In this manner, KineMed recently measured the proteome dynamic signature of a variety of cell types and conditions in mice, including liver mitochondrial proteins after long-term CR, muscle proteins after anabolic and catabolic interventions, hippocampal progenitor cell proteins in response to neurogenic agents and, in humans plasma proteins in healthy controls and CSF proteins in Parkinson's disease patients. The "unsupervised" or non-hypothesis-driven nature of the proteome dynamics approach allows discovery of previously unsuspected molecular targets, while the functional interpretability of many protein dynamic processes allows subsequent focus on specific targets of interventions. This new combination of proteomics with kinetics is unique to KineMed and has the power to see much deeper into the biology of the disease than a single readout such as collagen turnover.

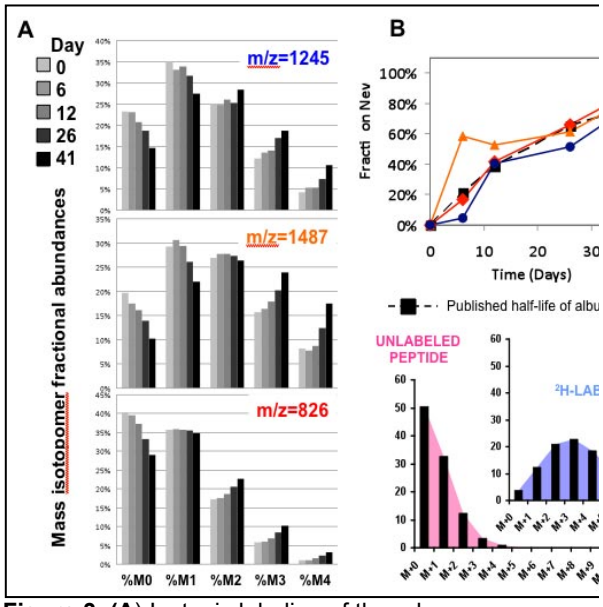


Figure 3. (A) Isotopic labeling of three human serum albumin peptides in vivo over time showing the relative increase in heavier mass isotopomers (M2 and above) and the decrease in light mass isotopomers (M0, M1). **(B)** The fractional synthetic rate of the same peptides over time. **(C)** Representative mass isotopomer distribution of an unlabeled and labeled peptide, showing the shift in centroid mass.

	Rate (Day^{-1})	
Retinol-binding protein 4	0.97	N-acetylmuramoyl-L-alanine amic
Apolipoprotein E	0.93	Fibrillin-3
Clusterin	0.90	Titin
Apolipoprotein C-III	0.79	Ficolin-3
Vitronectin	0.76	Complement C1q subcomponent
Complement C1r subcomponent-like protein	0.74	Fibrinogen alpha chain
Complement C1r subcomponent	0.69	Complement C1q subcomponent
Apolipoprotein A-IV	0.66	Fibrinogen gamma chain
Insulin-like growth factor-binding protein complex	0.62	Complement C1q subcomponent
Selenoprotein P	0.59	Complement factor H
Beta-2-glycoprotein 1	0.57	Corticosteroid-binding globulin
Fibronectin	0.49	Fibrinogen beta chain
Pigment epithelium-derived factor	0.48	Ceruloplasmin
Coagulation factor X	0.47	Hemopexin
Inter-alpha-trypsin inhibitor heavy chain H4	0.46	Serotransferrin
Inter-alpha-trypsin inhibitor heavy chain H1	0.41	RRN3-like protein 1
Angiotensinogen	0.41	Ig mu chain C region
Complement C1s subcomponent	0.40	TLD domain-containing protein K
Antithrombin-III	0.39	Putative hydroxypyruvate isomera
Complement C2	0.38	Alpha-2-macroglobulin
Kallistatin	0.38	Serum paraoxonase/arylesterase
Zinc-alpha-2-glycoprotein	0.37	Serum albumin

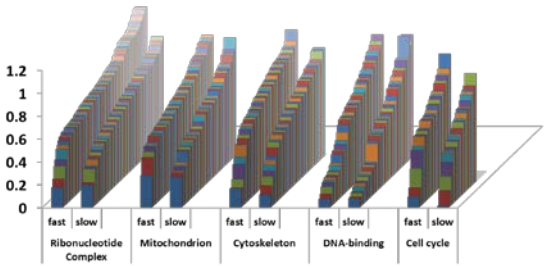
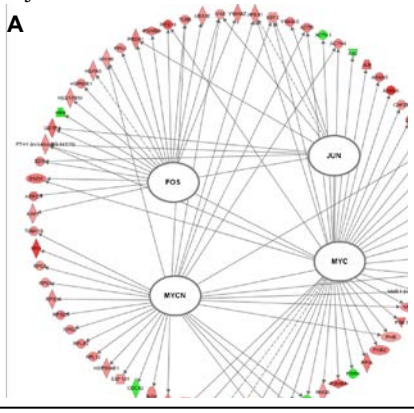


Figure 4: Dynamic proteomic analysis of slow vs. fast B-CLL. 440 protein synthesis rates measured in fast and slow subject. Up-regulated proteins synthesis rates in the fast subjects in gene ontology groups corresponding to cell proliferation and cell cycle.

KineMed has developed a technique for measuring cell proliferation rates *in vivo*, based on ^2H_2O labeling and mass spectrometric analysis, which has been applied to the measurement of the proliferation of numerous cell types in experimental animals and humans (original KineMed CLL cell proliferation biomarker)[11]. Cell proliferation is commonly measured via [^{3}H]thymidine or BrdU techniques, which are known to have toxic effects in animals, while ^2H_2O can be safely administered for long periods of time in drinking water. Currently, our published methods using ^2H_2O labeling are the only techniques for measurement of global protein turnover (dynamic proteomics) in rodents or humans. Our laboratory has successfully combined ^2H_2O labeling with LC-MS/MS analysis of tryptic peptides to quantify the turnover of cellular proteins *in vivo*[8]. These methods are well suited for the measurement of cell and protein proliferation in slow turnover tissues because ^2H_2O can be conveniently administered for long periods of time in drinking water, combined with the high sensitivity of mass spectrometric analysis of tryptic peptides[12]. Using ^2H_2O labeling in combination with cell proliferation analysis and dynamic proteomic techniques, KineMed proposed measuring the *in vivo* turnover rate of the B-CLL proteome before and after Pharmacyclixs treatment.

KineMed previously measured CD19+/CD5+ isolated cell pellets from subjects that were recruited and labeled as part of the KineMed and CRC cell proliferation biomarker clinical trial (Figure 4 and 5) and measured protein and DNA on selected subjects. They feel that a dynamic proteomic analysis of the Pharmacyclixs cells would provide additional information. Since protein turnover occurs more rapidly than cell division they may be able to label for less time than needed for the cell proliferation biomarker. KineMed will use the dynamic proteomics techniques they recently developed[9] to fully define the kinetics of the CLL B cell. Specifically, they plan to measure the turnover rates of a large number of proteins and correlate them against the DNA turnover rates to generate a complete kinetic profile of the CLL B-cell.

Figure 5: Network analysis of protein synthesis rates from fast vs. slow subjects
A) Ingenuity analysis of transcription factors responsible for protein up-regulation observed in the fast CLL subject



2.4 Results in CLL

Nicholas Chiorazzi and his colleagues at The Feinstein Institute for Medical Research of the North Shore - LIJ Health System have used the technique to successfully determine the kinetics of CLL cells in subjects [11]. Nineteen subjects imbibed heavy water for 12 weeks, and blood was collected at multiple time points during and after heavy water ingestion. CLL cells were isolated and analyzed for GC/MS analysis. The kinetic studies revealed significantly higher levels of proliferation than expected, with subject to subject variation in CLL birth rates ranging from 0.1% – 1.7%/day. Those subjects with a more rapid rate (defined as > 0.35%/day) were more likely to have progressive/active disease (8/10) than subjects with lower birth rates (< 0.35%/day) (1/9), as defined by the NCI-Working Group criteria [13].

2.5 PCI-32765

Antigenic stimulation through the BCR promotes expansion of CLL and other malignant B cells [14,15]. Btk, a key component of BCR signaling, can be blocked by PCI-32765, a small-molecule Btk inhibitor that displayed activity in subjects with CLL and other B cell malignancies in the first clinical trial [16]. PCI-32765 is a potent (IC50, 0.5nM) and selective Inhibitor of Btk that binds covalently to a cysteine residue (Cys-481) in the active site of Btk, leading to irreversible inhibition of its enzymatic activity [17]. Once daily oral dosing results in 24-hour sustained target occupancy. *In vitro* studies demonstrated that inhibition of Btk in CLL cells blocks BCR-related survival signals, thereby leading to apoptosis [18]. Additionally, Dr. Jan Burger's laboratory at MD Anderson Cancer Center has demonstrated that inhibition of Btk with PCI-32765 markedly decreases CLL cell responses to chemotactic factors elaborated by stromal cells, such as CXCL12 and CXCL13, resulting in diminished CLL cell migration and homing capabilities [18]. A recent analysis of data from 38 CLL subjects involved in an ongoing Phase Ib/II trial of single-agent PCI-32765 in CLL or SLL included subjects with relapsed or refractory disease following at least 2 treatment regimens, and a cohort of subjects over 65 years old with treatment naïve disease [16]. When measured clinically and by CT scan every 2 months, subjects treated with PCI-32765 typically had an immediate and marked nodal response; 87% of subjects with evaluable nodal disease achieved a nodal response. There have been no cases of primary lymph node progression. For the Phase Ia trial with a median follow-up of 8 months, there were 13 evaluable subjects with 1 CR (8%), 8 PRs (62%) and 2 subjects with a nodal response with lymphocytosis (15%). Two additional subjects had stable disease. There have been only 3 subjects with disease progression, and an additional 3 subjects discontinued treatment for reasons other than progressive disease. Of 32 evaluable subjects in the Phase Ib study (with less than 2 months median follow-up), there were 8 PRs (25%) and an additional 17 subjects with a nodal response with lymphocytosis. An additional two subjects have stable disease. As such, the overall response rate (ORR) from the Phase Ib/II trial experience at this point is 38% (1 CR, 16 PRs in 45 subjects). Ninety-four (94) percent of subjects experienced an adverse event (AE); 38% subjects experienced an adverse event grade 3 or greater in severity (nausea, vomiting, fatigue, diarrhea, headache, rash). The incidence of ≥ grade 3 AEs believed to be related to PCI-32765 was 17%. Fourteen subjects experienced a serious adverse event (SAE), with "serious" defined as requirement for hospitalization. Seven SAEs were considered related to study

drug by the investigator. These were one case of viral lymphadenitis, one case of a subdural hematoma, one case of viral infection (follow-up reported as unrelated), one case of decreased appetite, dehydration, and asthenia, one case of sepsis, and one case of headache and dizziness (follow-up reported as unrelated viral vestibular neuritis) and one case of hemorrhagic colitis [16]. Two subjects in this pooled analysis died from progressive disease. Diarrhea, nausea, and fatigue have been the most commonly reported AEs; with most of these occurring early in treatment (cycles 1 or 2). Significant myelosuppression has been infrequent; with grade 3 or greater thrombocytopenia or neutropenia reported in less than 5% of subjects. Significant hepatic or renal toxicity has been absent. In addition, with longer-term follow-up, there has been no evidence of cumulative toxicity, either overall or related to specific events. Because of the controversial role of Btk in platelet function and aggregation, subjects with a history of bleeding diathesis or coagulopathy, recent surgical procedure, stroke, or hemorrhage, and subjects receiving Coumadin will be excluded.

3.0 Adverse Events

PCI-32765 Serious Adverse Events

Allergic reaction: A dose limiting toxicity (DLT) hypersensitivity reaction occurred in the first-in-human study. Rash and petechiae have been reported in 13% of subjects. Most reports of rash and petechiae have been mild to moderate, however the DLT of hypersensitivity suggests that the potential exists for a more severe reaction in sensitive individuals.

Leukocytosis in CLL/SLL: An initial leukocytosis is often observed in subjects with CLL/SLL treated with PCI-32765; the leukocytosis decreases steadily over time.

**Of note, an initial leukocytosis has been observed in subjects with CLL/SLL treated with PCI-32765; the leukocytosis decreases steadily over time. The leukocytosis is postulated to be a pharmacodynamic effect of PCI-32765 causing lymphocytes to migrate to the blood from the lymph nodes, as substantial decreases in lymph node size have been observed to correlate with the leukocytosis. This phenomenon will be a prime analysis of the heavy water approach.*

Infections: Six subjects have had pneumonia as an SAE. Although pneumonia is a common infectious complication in subjects with lymphoid malignancy, a relationship to study drug cannot be ruled out at this time. Two subjects reported Viral Lymphadenitis.

Asthenia: was reported by one subject

Dehydration and Decreased Appetite: Was reported by one subject.

Subdural Hematoma: One subject developed a subdural hematoma.

Hemorrhagic Colitis: Seventy-three year old female developed, grade 3 diarrhea 9 days after starting study drug. The diarrhea progressively worsened and was hospitalized for hemorrhagic colitis. The Investigator assessed the event as possible related to study drug.

Common adverse events:

Heavy Water:

^2H_2O also occurs naturally, and a minor component of the water ingested daily contains ^2H_2O. The only known side effect of ^2H_2O ingestion, at the amounts to be ingested in this study, is a sense of lightheadedness. Less frequently, vertigo may occur when the compound is ingested too rapidly; this lasts until equilibration within the semi-circular canals of the ear is reached. In the unlikely event that dizziness occurs, it usually subsides spontaneously within three hours.

PCI-32765:

So far, the most commonly reported treatment-emergent adverse events considered related to PCI-32765 have been diarrhea (29%), fatigue (17%), nausea (11%), vomiting (9%), and rash (8%). Most of these events also have been mild to moderate in severity.

The above is preliminary safety information. The information has been reviewed, but has not been completely monitored; therefore, minor changes to the safety information may occur going forward. Safety information will continue to be collected and evaluated as the study continues.

There were seven (7) deaths within 30 days of last dose of PCI 32765 as of 1/4/11. All deaths were due to disease progression and were reported as unrelated to PCI 32765.

Potential for Drug-Drug Interactions

Because these PCI-32765 IC50 values are markedly higher than the plasma levels of unbound PCI-32765 observed for the initial Phase 1 clinical study, inhibition of P-gp transport and CYP450 isoenzyme metabolism is not expected to occur in humans.

However, PCI-32765 is extensively metabolized by CYP2D6 and CYP3A4. Therefore, any medications that are strong inhibitors of CYP2D6 and/or CYP3A4 (eg, itraconazole, ketoconazole, clarithromycin, and bupropion) should be administered with caution and only after consultation with the Medical Monitor.

4.0 Objectives

The primary objective is to assess the impact of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 on leukemia cell trafficking and death using heavy water (^2H_2O) labeling of newly-born malignant cells in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).

The secondary objective is to determine the percent of recently born versus older leukemia cells mobilized into the blood by PCI-32765 treatment.

The tertiary objective is to compare the kinetic biomarker measurements in CLL subjects to other established prognostic tests and response to therapy with PCI-32765.

5.0 Study Design

This is a one center, open label pilot study to evaluate the impact of the Btk inhibitor PCI-32765 on leukemia cell trafficking and death, using heavy water labeling in subjects with Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). PCI-32765 will be supplied by Pharmacyclics as capsules containing 140mg of PCI-32765. Subject grade $^{2}H_2O$ will be purchased from KineMed, Inc, and KineMed will analyze *in vivo* incorporation of ^{2}H into deoxyadenosine of B lymphocytes by GC/MS. A total of 30 subjects are to be enrolled at MD Anderson Cancer Center.

6.0 Subject Eligibility

Inclusion Criteria:

Subjects will be eligible for inclusion in the study if they meet all of the following criteria:

1) A diagnosis of CLL/ SLL and have not been previously treated.
2) An indication for treatment by 2008 IWCLL Criteria
3) Male and female subjects of age $\geq$ 18 years at the time of signing informed consent and requiring treatment within the next 2 to 6 months.
4) Understand and voluntarily sign an informed consent, and be able to comply with study procedures and follow-up examinations.
5) Platelet counts at study entry must be greater than 50,000/μL and absolute neutrophil counts at study entry must be greater than 750/μL
6) Free of prior malignancies for 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
7) Subjects must be able to contribute the required amount of blood and/or tissue without compromising their well-being or care and must weigh at least 110 pounds
8) Adequate renal and hepatic function as indicated by all of the following: total bilirubin </=1.5 x institutional Upper Limit of Normal (ULN); AST or ALT </=2.5 x ULN; and estimated creatinine clearance (CrCl) of > 30 mL/min, as calculated by the Cockroft- Gault equation
9) Participants must be willing to be contacted again for consideration of additional studies in the future, such as a blood draw or another action (e.g., bone marrow aspiration and/or biopsy) that would be associated with their standard of care, unless they consented to such for research purposes.
10) An ECOG/WHO performance status of 0-2.
11) Males and females of child bearing potential must have adequate birth control protection while on study and for 30 days after the last dose of study drug. The couple will use two forms of birth control for the entire time of the study and 30 days after finishing study. Conception control should include a hormonal method (birth control pill, etc.), and a double-barrier methods (condoms with spermicidal, sponge with spermicidal, or diaphragm with spermicidal), or abstinence (not having sex) will be practiced.
12) Female subjects will need a negative pregnancy screening test if they are of child bearing potential.

Exclusion Criteria:

1) Subjects less than 18 years of age
2) A lymphocyte doubling time of < 3 months, or other clinical or laboratory signs indicating that a treatment delay of 2 months or longer (due to heavy water labeling and resting period) would result in a significant progression of the disease and be detrimental to the subject, as determined by the treating physician
3) Any prior treatment for CLL including chemotherapy, chemoimmunotherapy, monoclonal antibody therapy, radiotherapy, or high-dose corticosteroid therapy (Prednisone > 60 mg daily or equivalent), or immunotherapy prior to enrollment or concurrent with this trial.
4) Concomitant use of agents that have been described to affect the biology and/or proliferation rate of CLL cells such as: PDE-inhibitors (e.g., sildenafil, theophylline), immunosuppressive agents (e.g., prednisone, cyclosporin-A, rapamycin), green tea extract, itraconazole, ketoconazole, clarithromycin, bupropion, and Cox-2 inhibitors
5) Investigational agent received within 30 days prior to the first dose of study drug. If received any investigational agent prior to this time point, drug-related toxicities must have recovered to Grade 1 or less prior to first dose of study drug.
6) Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
7) Subjects with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP)
8) Any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver or other organ system that may place the subject at undue risk to undergo therapy with PCI-32765.
9) Any serious medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study.
10) History of intracranial hemorrhage or stroke within 6 months prior to the study
11) Evidence of bleeding diathesis or coagulopathy
12) Major surgical procedure, open biopsy, or significant traumatic injury, within 28 days prior to Day 1, anticipation of need for major surgical procedure during the course of the study. (Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1. Bone marrow aspiration +/- biopsy is allowed).
13) Serious, non-healing wound, ulcer, or bone fracture.
14) Subjects receiving anticoagulation (for example heparin, Coumadin, low-molecular-weight heparin (LMWH, such as Lovenox), and anti-platelet drugs (except for low-dose aspirin) will be ineligible to participate in this study. Subjects who recently received drugs for anticoagulation must be off those medications for at least 7 days prior to start of the study.
15) Subjects who are known to be anemic, with hemoglobin <8.0g/dl.
16) Weight less than 110 pounds
17) PCI-32765 is contraindicated in subjects with clinically significant hypersensitivity to any of the compound's structural components.

18) Subjects who are known to be infected with HIV, or have signs of active Hepatitis B or Hepatitis C
19) Biliary obstruction, acute hepatitis, severe liver failure, or severely impaired renal function

7.0 Pretreatment evaluation

Pretreatment evaluation will include a physical examination including vital signs, ECOG/WHO performance status, height and weight, and recording of concurrent medications, and will be done within 30 days prior to day 1 (See Appendix A).

Clinical laboratory evaluation will involve serum chemistries, including sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, andBeta-2-microglobulin levels Hematology studies will include complete blood count (CBC) with differential and peripheral blood lymphocyte subset analysis, immunoglobulin levels (within 30 days prior to day 1), and coagulation studies (Prothrombin Time/PT; Partial Thromboplastin Time/PTT; and International Normalized Ratio/ INR) within 30 days prior to day 1. Flow cytometry assessment for peripheral CLL cells (CLL panel) and lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16/56 cells, 30 days prior to day 1).

Bone marrow aspiration and biopsy will be obtained within one month of day 1 of the study, and again after 3, 6, and 12 cycles (+/- 1 month), only bone marrow aspirations (no biopsy) will be done during follow-up evaluations after 3, 6, and 12 cycles) after initiating PCI-32765 therapy. The screening bone marrow will be evaluated by flow cytometry for clonality and for *IGHV* mutation studies (unless known), CD38 expression, ZAP-70 expression, and cytogenetic and genomic abnormalities by FISH. Follow-up bone marrow tests after 3, 6, and 12 cycles (+/- 1 month) will evaluate morphology (bone marrow lymphocyte quantification), and quantification of CLL cells by flow cytometry, including minimal residual disease assessment by flow cytometry. Electrocardiogram (within one month from registration) will be required. We will not require additional ECG monitoring during this study. As of April 6, 2012, 408 subjects have been treated with ibrutinib in 8 clinical studies. The cardiovascular safety of ibrutinib was evaluated by monitoring of adverse events in all studies; in addition, a formal ECG monitoring was performed in 2 studies (PCYC-04753 & PCYC-1102-CA). To date there is no evidence of ECG morphological changes or prolongation of QTc in patients treated with ibrutinib. The most common cardiovascular adverse events reported across the studies were atrial fibrillation (n=17), tachycardia (n=7), sinus tachycardia (n=4) and sinus bradycardia (n=3). Events of Grade 3 or greater severity included only atrial fibrillation (n=6), supraventricular tachycardia (n=2) and tachycardia (n=1). These findings are consistent with expectations in elderly population of subjects many of whom have known cardiovascular disease at baseline. Because of these data we will not request follow-up ECGs. Subjects also will undergo CT scans of the chest, abdomen, and pelvis after 3 or 6 cycles (+/- 1 month) and after 12 cycles (+/- 1 month) of PCI-32765 therapy.
Anti-coagulated blood sample (50ml) and coagulated blood sample (10ml) for baseline $^{2}H_2O$ studies on the day of study initiation (Day 1).

8.0 Treatment Plan

8.1 Heavy Water Protocol: Labeling phase.

After enrollment and a baseline blood draw (60ml), subjects will start to consume heavy water (^2H_2O). Subjects will be given 50 mL of 70% ^2H_2O 3 times a day for the first 5 days followed by 60ml daily for a total of 4 weeks (labeling phase). Lightheadedness or dizziness may occur for some subjects (~15%) with the initial doses; therefore subjects will be given their first dose in clinic and asked to avoid driving or performing potentially hazardous activities for one hour. If such symptoms occur, they usually abate within 2-3 hours. Subjects will then be given individual doses of ^2H_2O to consume at home; after the 5-day loading period, a 60 mL maintenance dose of ^2H_2O will be drunk at bedtime to obviate any problems with dizziness. Compliance with ^2H_2O ingestion will be documented using a heavy water ingestion diary (intake logs). Unused ^2H_2O will be returned for disposal.

Subjects will be seen at day 1 (+/- 3 days), day 14 (+/- 3 days), and day 28 (+/- 3 days) after beginning ^2H_2O ingestion for follow-up visits with clinical and laboratory assessment, which will include determining if there have been any problems with ^2H_2O ingestion, analysis and discussion of intake logs, and blood sampling (60ml) for CLL cell kinetic measurements (heavy water testing).

8.2 Heavy Water Protocol: Resting phase.

At the end of the 4th week, subjects will stop drinking ^2H_2O (washout phase) and be followed for 6-12 weeks until beginning treatment with PCI-32765. During the period until initiation of therapy, subjects will be seen every 2 weeks (+/- 3 days) for follow-up visits with clinical and laboratory assessment. Blood will be drawn at the same time every 2 weeks (+/- 3 days), to determine a disappearance rate (death plus re-distribution into solid tissue) of CLL cells containing ^2H-labeled DNA. Only those subjects that have not imbibed ^2H_2O for at least 6 weeks from the end of the labeling period until starting on treatment with PCI-32765 or those patients who have not imbibed heavy water for less than 6 weeks and have received study PI approval will be included in further ^2H_2O kinetic studies, although they will receive PCI-32765 as a part of the response to therapy studies. After start of treatment with PCI-32765, there will be blood sampling (60ml) for CLL cell kinetic measurements (heavy water testing) on days 1 (+/- 3 days), 3 (+/- 1 day), and then at week 2 (+/- 3 days) and every 2 weeks (+/- 3 days) thereafter for a period of at least equal in duration to that of the initial ^2H_2O washout phase (6 to 12 weeks). Patients will continue to return to clinic each month for blood drawing (60ml). Data obtained from these blood samples will permit a determination of CLL birth rate as well as a slope of labeled cell emergence from solid tissue into the peripheral blood.

8.3 Treatment with PCI-32765

PCI-32765 will be administered with 8 ounces (~240mL) of water at a dose of 420 mg (3 x 140mg capsules) orally once daily and will be continued daily. A PCI-32765 dose of 420 MG PO once daily is based on the experience in Phase 1 and Phase 2 trials which established this dose and schedule to be adequate to induce BTK target occupancy (see

Advani et al, JCO 2012[19]). 420 mg is the dose used in all of the CLL/SLL trials to date. Each dose of PCI-32765 should be taken at least 30 minutes before eating and at least 2 hours after a meal at approximately the same time each day. Subjects will be instructed to avoid grapefruit juice due to CYP450 3A4 inhibition. Compliance with PCI-32765 ingestion will be documented using a diary. Treatment duration will be 12 cycles, with each cycle consisting of 28 days. Response will be evaluated after 3, 6 and 12 cycles. It will be possible for subjects to continue taking the drug beyond 12 cycles if there is a significant benefit such as an ongoing PR or CR. Unused PCI-32765 will be returned for disposal per institutional policy.

8.4 Special Handling Instructions

Allopurinol at the dose of 300mg daily will be given during the first one to two weeks of treatment as standard tumor lysis prophylaxis.

8.5 Concomitant Medication

Subjects receiving anticoagulation (for example heparin, Coumadin, low-molecular-weight heparin (LMWH, such as Lovenox), and anti-platelet drugs (except for low-dose aspirin) will be ineligible to participate in this study. Subjects who recently received drugs for anticoagulation must be off those medications for at least 7 days prior to start of the study.

8.6 Guideline for Use of CYP Inhibiting Drugs

PCI-32765 is metabolized by CYP3A4/5 and CYP2D6. Alternatives to strong CYP3A4/5 inhibitors (such as clarithromycin, ketoconazole, itraconazole, nefazodone, and ritonavir) and strong CYP2D6 inhibitors (such as bupropion, fluxetine, paroxetine, and quinidine) should be sought if possible.

If no alternative treatment is available, strong CYP3A4/5 and CYP2D6 inhibitors should be used with caution; patients should be closely monitored for potential toxicities with temporary interruption of PCI-32765 as appropriate.

A comprehensive list of cytochrome P450 isoenzymes and CYP3A4/5 and CYP2D6 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

8.7 Concomitant Use of QT Prolonging Agents

During the course of study drug treatment medications known to cause Torsades des Pointes should be avoided. Medications known to cause QT prolongation may be used with caution.

8.8 Concomitant Use of Antiplatelet Agents and Anticoagulants

Laboratory studies have shown that, in vitro, PCI-32765 can prevent platelets from aggregating normally; the clinical significance of this finding is unknown at this time. While serious bleeding has been uncommon in patients treated to date, it is possible that treatment with the study drug could increase the risk of bruising or bleeding, particularly in subjects receiving other antiplatelet agents or anticoagulants.

Subjects receiving antiplatelet agents in conjunction with PCI-32765 should be observed closely for any signs of bleeding or bruising, and PCI-32765 should be withheld in the event of any bleeding events.

Subjects requiring the initiation of anticoagulation with warfarin or related agents during the course of the study should have treatment with PCI-32765 held, and PCI-32765 should not be restarted until subjects are stably anticoagulated. During the co-administration of PCI-32765 and anticoagulant therapy, the INR should be monitored carefully and subjects should be observed closely for signs and symptoms of bleeding.

8.9 Sample Collections for ^{2}H-DNA-labeled Leukemic Cells during PCI-32765 Treatment Phase

After beginning PCI-32765 therapy, subjects will be seen for follow-up visits including blood draws (60ml) at day 1 (+/- 3 days), day 3 (+/- 1 day), week 2 (+/- 3 days), and every 2 weeks (+/- 3 days) thereafter for a period at least equal in duration to that of the initial $^{2}H_2O$ washout phase of 6 to 12 weeks. At these visits, clinical and laboratory assessment, which will include blood sampling (60ml) for $^{2}H_2O$ kinetic measurements, will be made. Subjects will continue to return or be seen by a local physician or clinical laboratory each month (+/- 3 days) for an additional 3 months for blood drawing (60ml). Data obtained from these blood samples will permit a determination of the slope and rate of the appearance of previously labeled CLL cells in the blood, and the slope and rate of the disappearance of labeled cells from the blood. If re-circulation to solid tissues is inhibited by PCI-32765 therapy, the disappearance rate will represent primarily the death rate of leukemic cells *in vivo*. Because during the treatment period, $^{2}H_2O$ will not be available to label newly-born cells, any cells containing ^{2}H-labeled DNA will represent cells labeled during the initial period of $^{2}H_2O$ consumption and retained in situ. The kinetic measurements of the entire CLL clone will be compared with those of intraclonal fractions from the same samples, defined by the reciprocal differences in CXCR4/CD5 surface membrane densities; this approach is described in the published study by Calissano et al. (Mol Med 2011;17: 1374-1382, 2011). In addition, these fractions will be analyzed for:

1. Phenotype and numerical changes of B and T cells and myeloid cells within these fractions, pre- and post-ibrutinib therapy
2. Gene expression profiles of cells within these fractions, pre- and post-ibrutinib therapy
3. DNA methylation profiles of cells within these fractions, pre- and post-ibrutinib therapy.

4. Response to BCR and other signals of cells within these fractions, pre- and post-ibrutinib therapy,using western blots on phosphoproteins/ibrutinib occupancy
5. Differences in engraftment and growth capacities of CLL B and T cells in NSG mice, unseparated or within these fractions, pre- and post-ibrutinib therapy

All data will be correlated with the kinetic data of the clone and its CXCR4/CD5 subsets in order to better characterize CLL cell subpopulations that are affected by PCI-32765 therapy and that account for CLL cell mobilization and/or proliferation. These additional analyses will be done at Dr. Chiorazzi's site, in collaboration with Dr. Burger and his colleagues at MD Anderson Cancer Center.

8.10 Outside Physician Participation during Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (see Appendix H)
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
8. Patients will return to MDACC every month for the first 3 months of starting treatment with PCI-32765, and then every 3 cycles for evaluation (every 6 months after cycle 36)

9.0 Special Instructions about Heavy Water Ingestion:

Related to heavy water

"Heavy water" is similar to "regular water" in taste, smell, and color. There are no known major harmful effects of heavy water when consumed in the amounts given in this study. Minor side effects include nausea, dizziness, lightheadedness, and vertigo. Participants will be advised to avoid performing activities such as driving, operating machinery, and exercise that could potentially compromise their safety immediately after drinking the heavy water. They should wait at least 60 minutes before resuming any strenuous activities. Unused $^{2}H_2O$ will be returned for disposal.

Special Instructions Related to contraception

Heavy Water:
Even though no pregnant women will be enrolled in this study, deuteriated compounds including deuteriated vitamin E, deuteriated nicotine, and deuteriated water have been given to pregnant women to study the physiology of pregnancy and no ill effects to mother or fetus have been observed.

PCI-32765:
The potential effects of PCI-32765 on a developing fetus have not been determined in animals or humans.

Therefore, if a woman of childbearing potential is enrolled in this study or a man with a partner who has childbearing potential, the couple will use two forms of birth control for the entire time of the study and 30 days after finishing study. Conception control should include a hormonal method (birth control pill, etc.), and a double-barrier methods (condoms with spermicidal, sponge with spermicidal, or diaphragm with spermicidal), or abstinence (not having sex) will be practiced.

10.0 Evaluation during Study

- **Clinic visits, end of treatment visit**

Each clinic visit will include vital signs and a physical exam. Physical examinations should include height (screening only) and weight, examination of the skin, eyes (with specific questions focused on ocular symptoms), ears, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system. The examination should also include inquiry of ocular symptoms and subjects should be referred to an ophthalmologist for a formal examination if any Grade > 2 symptoms are reported. After beginning PCI-32765 therapy, subjects will be seen for follow-up visits including blood draws (60ml) on days 1 (+/- 3 days), 3 (+/- 1 day), and then at week 2 (+/- 3 days), and every 2 weeks (+/- 3 days) thereafter for a period at least equal in duration to that of the initial 2H2O washout phase of 6 to 12 weeks. Subjects will return to clinic or will be seen by a local physician each month (+/- 3 days) for an additional 3 months for follow-up visits with clinical and laboratory assessment, including vital signs and physical exam, and laboratory workup, including hematology and clinical chemistry evaluations and then every 3 months (+/- 3 days) until the end of 12 cycles. If subjects stay on the study past 12 cycles, they will return for clinic visits for clinical assessment, including vital signs and physical exam, and laboratory workup, including hematology and clinical chemistry evaluations, very 3 months (+/- 1 month) for cycles 13 through 36, and every 6 months (+/- 1 month) thereafter. For patients that discontinue therapy with PCI-32765, an end of study visit at MD Anderson will be required. Patients will be followed for at least 2 months (+/- 1 month) after the last dose of PCI-32765 for assessment of adverse events. This will be done in a Leukemia Clinic visit that will be scheduled to occur at 1 month (+/- 10 days) after the last dose of PCI-32765.

- **Hematology and serum chemistry**

CBCs (white blood cell, hemoglobin, platelets and differential) will be monitored on days 1, 14, and 28 (+/- 3 days) and then every 4 weeks (+/- 3 days) thereafter. Serum chemistry including basic metabolic profile (sodium, potassium, chloride, CO2, BUN, creatinine and glucose) will be monitored once weekly (+/- 3 days) for the first 4 weeks and then once every 4 weeks (+/- 3 days) thereafter until the end of cycle 12. If subjects stay in the study past 12 cycles, they will have these laboratory tests (hematology and clinical chemistry) done every 3 months (+/- 1 month) for cycles 13 through 36, and every 6 months (+/- 1 month) thereafter during their clinic visit.

PT, PTT, and INR will be monitored after cycles 3 and 12 (+/- 1 week) and if subjects stay on the study past 12 cycles, once every 12 cycles (+/- 1 month).

- **Bone marrow testing, beta-2-microglobulin, lymphocyte subset, immunoglobulin levels**

Bone marrow testing will be done by flow cytometry after 3 (+/- 1 month), 6 (+/- 1 month), and 12 cycles (+/- 1 month) and if subjects stay in the study past 12 cycles, once every 12 cycles (+/- 1 month). Beta-2 microglobulin and immunoglobulin levels will be assessed at screening and at the timepoints specified in the study calendar (see calendar of events at the end of the protocol).

- **CT scans of the chest, abdomen, and pelvis**

These will be performed within 30 days before starting Heavy Water, and then after 3 or 6 cycles, and after 12 cycles. All other scans are at the treating physician's discretion.

- **Research Testing as an Optional Procedure**

  Patient samples (blood cells, DNA, RNA) will be analyzed by colleagues at the Dana-Farber Cancer Institute (DFCI), Boston (Dr. Catherine Wu and associates) for gene mutations within the CLL cells in patients responding or not responding to therapy with PCI-32765. These tests will allow us to determine why some CLL cells persist during therapy with PCI-32765 and why some patients have suboptimal responses or no response to PCI-32765. No additional blood draws will be necessary for these tests.

  Blood samples will be analyzed by Dr. Richard Eric Davis (Department of Lymphoma and Myeloma, MD Anderson) for changes in gene expression in CLL cells during therapy with PCI-32765. For these studies, one additional tube of blood (approximately 1 tablespoon per time point) will be collected on cycle 1, week 1, day 1 (+/- 3 days) before the start of PCI-32765, and day 3 (+/-1 day), and on week 4 (+/- 3 days), and week 12 (+/- 3 days), during therapy with PCI-32765.

Finally, a sputum sample will be collected on day 1 of week 1 (+/- 3 days) during follow-up which will serve as a control for the genetic testing of the leukemia cells.

Samples collected will be stored at Dr. Burger's laboratory and then sent to the Dana-Farber Cancer Institute

- **Confidentiality**

  All patient-identifying information will be removed from all samples before being sent to DFCI and Dr. Richard Davis' laboratory and will only be available to the PI at MD Anderson, Dr. Jan Burger.

11.0 Criteria for Response

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria will be used [20]. Responses will be assessed after 3, 6 and 12 cycles.

12.0 Evaluation of Toxicity

Safety Results Among Treatment-naïve Elderly Patients
The safety profile of treatment-naïve elderly patients receiving PCI-32765 has been consistent with the treated population as a whole, as evidenced by the 31 patients aged 65 years or older in Study PCYC-1102-CA (data cut 03 July 2012). Diarrhea (58%), nausea (50%), and fatigue (35%) have been the most prevalent treatment-emergent AEs. Of the 31 treatment-naïve CLL patients aged 65 years or older in study PCYC-1102-CA, 42% experienced a Grade 3 or 4 AE (32% and 10%, respectively). Three patients had Grade 3 diarrhea. The only Grade 4 AEs were anemia, thrombocytopenia, and neutropenia (1 patient each). Two out of the 31 elderly patients (6.5%) experienced an AE leading to study drug discontinuation in Study PCYC-1102-CA. The AEs leading to discontinuation were Grade 2 viral infection and Grade 3 fatigue. One patient, a 75-year-old man, was hospitalized for symptoms of a viral illness that began 35 days after the start of study treatment and resolved during the hospitalization. Study drug was discontinued due to non-serious symptoms of night sweats and fever that persisted past drug discontinuation and were attributed to CLL. The other patient, a 70-year-old woman with a medical history of hypothyroidism and intermittent fatigue, was treated with study drug for approximately 4 months and had achieved a partial response with lymphocytosis. Study treatment was discontinued due to Grade 3 fatigue.

Of note, serial evaluation of quantitative serum immunoglobulins in both relapsed/refractory and treatment-naïve elderly patients revealed a statistically significant increase in IgA at 3, 6, and 12 months ($p<0.005$ at each timepoint, multiplicity not adjusted) with no decline in IgG or IgM, indicating that PCI-32765 did not impact normal immunoglobulin production.

Assessment of Safety
Safety assessments will consist of monitoring and recording AEs and SAEs, and should be consistent with institutional standards and Good Clinical Practice.

Adverse Events

An AE is any untoward medical occurrence in a subject 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 an 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.

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

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.

- Any adverse events experienced by the subject through the completion of final study procedures.

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MCL 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 an adverse event:

- **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.

- **Preplanned 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. Hospitalizations for social reasons or due to long travel distances are also not SAEs.

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

Suspected Adverse Reaction

A Suspected Adverse Reaction is any adverse event for which there is a “reasonable possibility” that the drug caused the adverse event.

"Reasonable Possibility", for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the drug and the adverse event. Examples of evidence that would suggest a causal relationship between the drug and the adverse event are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (eg, strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the sponsor could make a determination of whether the drug caused the event.

- An aggregate analysis of specific events that can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (eg, symptoms or disease progression), or events unlikely to be related to the underlying disease or condition under investigation, but commonly occur in the study population independent of drug therapy (eg, cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the drug treatment group than in a concurrent or historical control group.

Severity

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

The investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event).

Unexpected

An "unexpected" AE is an AE that is not listed in the Investigator Brochure 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 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 Brochure listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator 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.

Serious Adverse Event Reporting (SAE) for MD Anderson sponsored IND Protocols

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).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- 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 Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- 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.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

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.

Protocol-specific dose adjustments

PCI-32765 dose adjustments for surgical or invasive procedures:

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.

PCI-32765 dose adjustments for the following hematologic toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days
- Grade 3 or 4 Platelets (< 50,000/μL) in presence of significant bleeding
- Grade 4 Platelets (< 25,000/μL)

Gastrointestinal toxicities:

- Grade 3 or 4 nausea, vomiting or diarrhea if persistent despite optimal antiemetic and/or anti-diarrheal therapy) or any other grade 4 or unmanageable grade 3 toxicities:

Occurrence	Action
1st	**Hold PCI-32765 until recovery to Grade ≤ 1 or baseline; may restart at original dose level**
2nd	**Hold PCI-32765 until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)**
3rd	**Hold PCI-32765 until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily)**
4th	**Discontinue PCI-32765**

Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Pharmacyclics within 24 hours of awareness following the procedure described for SAEs and will require enhanced data collection. All Events of Special Interest will be submitted without a serious criterion selected if no other serious criterion is met.

List of Events of Special Interest

Major Hemorrhage

Defined as any hemorrhagic event, that is Grade 3 or greater in severity, or that results in one of the following: intraocular bleeding causing loss of vision, the need for a transfusion of two 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 (see above).

DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed are reported during the study.

Adverse Event Reporting Period

The AE reporting period for this study begins when the patient takes the first dose of study drug and ends with the safety follow-up visit If an SAE is present at the safety follow-up visit, or within 30 days of the last dose of study drug (whichever is later), the SAE (and associated AEs and concomitant medications) should be followed to resolution or until the Investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the patient's medical record and on the CRF and, when applicable, on an SAE form.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see following guidance), and any actions taken.

All SAEs (initial and follow-up information) will be reported by the investigator, or designee, to Pharmacyclics, within 24 hours, or the next business day, after discovery of the event or information. The sponsor and Pharmacyclics may request follow-up and other additional information (eg, hospital admission/discharge notes, and laboratory results).

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. The primary cause of death on the autopsy report should be the term reported.

An SAE will qualify for expedited reporting to regulatory authorities if the SAE is considered a Suspected Adverse Reaction and is not listed in the current Investigator's Brochure (ie, an unexpected event).

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Fatal:	Adverse event resulted in death.
Unrelated:	Another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, but the adverse event 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 adverse event causes.
Definitely Related:	The adverse event is clearly related to use of the investigational product.

Pregnancy

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

A patient must immediately inform the investigator if the patient or patient's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. Any female patients receiving PCI-32765 who become pregnant must immediately discontinue study drug. The investigator should counsel the patient, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on appropriate case report form and fax it to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. The pregnant female will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE. .

Expedited Reporting Requirements for SAEs and Fatal or Life-Threatening Suspected Adverse Reaction Reports

Investigators of studies conducted under an IND must comply with the following safety reporting requirements.

The investigator must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review and archive. A copy of this IND safety report must also be faxed to Pharmacyclics Drug Safety.

The investigator must notify FDA and Pharmacyclics of any serious, unexpected, suspected adverse reaction observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of the occurrence.

The investigator must notify FDA and Pharmacyclics of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but no later than 7 calendar days after the Sponsor's receipt of the information.

Upon request from the FDA or Pharmacyclics additional data or information that the agency or Pharmacyclics deems necessary, must be reported as soon as possible but no later than 15 calendar days.

FDA Contact	
Pharmacyclics Drug Safety Contact Information	
US Local Fax:	1-760-268-6500
US Toll Free Fax:	1-877-676-0330

13.0 Statistical Considerations

The primary objectives of the statistical analysis will be (1) to demonstrate that there is a population of CLL cells that do not leave or take sanctuary outside of the peripheral blood system in solid lymphoid tissues, (2) to describe the longitudinal pattern in observed labeled cells and (3) to estimate rates of cell death.

For purposes of statistical analysis, the experiment will be divided into two periods (with each period, itself, being divided into two subperiods): Period 1 corresponds to the non-interventional period when heavy water is consumed for 4 weeks (Period 1a) and then discontinued (Period 1b) so that a CLL cell disappearance rate can be tracked over time.

Period 2 corresponds to the interventional period when Btk inhibitor (PCI-32765) is administered to subjects. Assuming that the observed percentage of labeled cells (LC) reaches a peak at some point in time, T, then Period 2a is defined as the "pre-peak" sub-period (i.e., all times $t \leq T$) and Period 2b is the "post-peak" sub-period ($t > T$).

Strictly speaking, Period 1 does not enter into any statistical analysis, as it only serves to provide labeling for the cells that allegedly remain and return and are retained in solid tissues. However, Period 1 will permit definition of CLL cell birth rate and disappearance rate (death and permanent return to solid tissue from blood).

An important part of the statistical analysis in Period 2 is characterization of the pattern of LC over time. Patterns will be analyzed both visually and using more formal statistical methods in an exploratory manner. First, the pattern will be smoothed using a cubic spline interpolation (SAS Graph, SAS Institute, Cary, NC). This will facilitate the determination of shape and numbers and patterns of peaks by eliminating "noise" in the data. Second, based on the patterns observed after smoothing, the data will be fit to candidate regression models (e.g., parabolas, mixtures of parabolas, piecewise curves, etc.) and the best fitting model will be identified using common statistical methods such as R^2, Akaike's information, etc. All curves will be fit on individual subjects, thereby permitting subjects to vary in the pattern of their LC response curves.

For example, one possible pattern would be an inverted-U parabola (Figure 1), where LC initially increases (presumably, as previously labeled CLL cells are simultaneously retrieved from solid tissue sanctuaries) and then declines (as the solid tissue sanctuaries have been depleted). Another example would be a mixture of two inverted-U parabolas (Figure 2), whereby there are two distinct peaks, suggesting that retrieval of cells from solid tissue may take place at two distinct times. Clearly, many other patterns are possible; however, the most likely candidate patterns are those with some form of initial upward slope, followed by a global peak, followed by a downward slope.

Interim analyses and stopping rules: In order to monitor study progress and success, interim analyses will be done after the first 5 and the first 10 patients have been labeled and treated for 3 months. The study will be placed on hold if the interim analyses determine that in less than 3 out of 5 patients or in less than 6 out of 10 patients, sufficient kinetic biomarker measurements can be obtained to accomplish the study

objectives (for technical and other reasons, such as patient compliance). In this case, the study would need to be modified and can only be re-opened after a protocol revision that addresses such potential technical and/or logistical issues, which needs to be agreed upon among the Principal Investigators and the sponsor. At that time, the investigators together with the sponsor will determine whether the data indicate that the objectives of the study can be met, or whether substantial changes to the protocol or data analyses would become necessary. This interim analysis will, however, not place the patient accrual on hold, unless the interim analyses would come to the conclusion that the study needs to be modified. In addition, at any time during the trial, if we see more than 30% of patients experiencing grade 3-4 non-hematological toxicities, we will stop the trial.

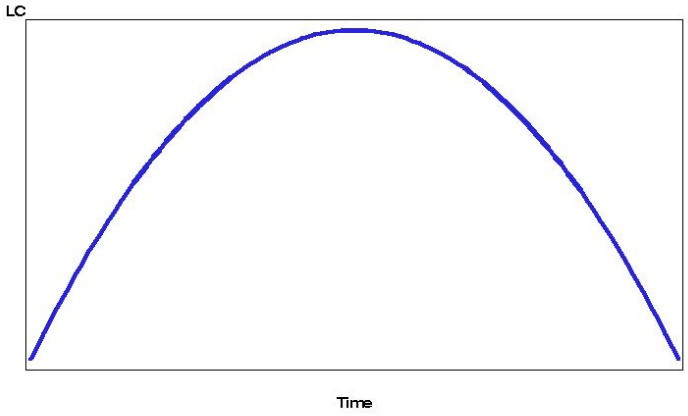


Figure 1 - An Inverted-U Parabola

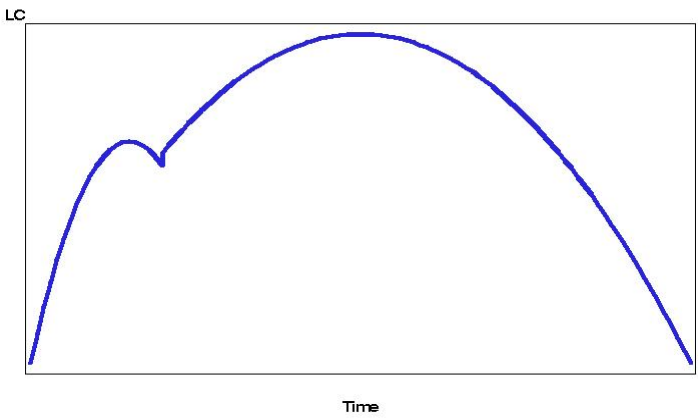


Figure 2 - Mixture of 2 Inverted-U Parabolas

In general, no formal statistical inference is planned (i.e., hypothesis tests or confidence intervals). The analysis is exploratory with the primary objective of discovering patterns of observed labeling that might provide further insights into the kinetics and biology of CLL.

14.0 Sample Size Considerations

This is primarily a (structured) exploratory study to discover patterns of cell kinetics in CLL. There are no data from previous experiments that would permit specification of a formal alternative hypothesis for which a power or precision calculation could be made. The proposed sample size is 30 subjects of which it is expected that 18 (approximately 60%) will be evaluable. An evaluable patient for the purpose of this protocol is primarily defined as a patient who has been able to adhere to all protocol-required procedures and blood draws during the heavy water labeling period, the resting period, and during treatment with PCI-32765. In addition, to be considered an evaluable patients, sufficient material with detectable levels of heavy water-labeled CLL cells must be recovered from the blood specimen by our colleagues at the Feinstein Institute and at KineMed, Inc. Specifically, it is expected that about 20% of subjects will exhibit a delayed release of labeled cells into the circulation in Period 1, which will manifest itself as an initially "flat" response; this number is based on available information from previous studies of this type. These subjects will be excluded from both the Period 1 and 2 analyses, but may be analyzed separately. In addition, it is anticipated that 20% of subjects will not be able to delay treatment for the desired 12-16 weeks post-labeling. These subjects will also be excluded from both the Period 1 and 2 analyses, but their data may be analyzed and used separately. The proposed sample size is consistent with other studies in CLL using similar methodologies. If necessary, the overall accrual will be increased in order to yield at least 20 evaluable subjects.

15.0 References

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Schedule of Events

Evaluation or Procedure	Screening (30 Days)	Treatment Plan Heavy Water (^2H_2O) Week 1	Week 2,4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Clinical Assessments	Day -30 to -1	Day 1	Day 14, Day 28	Day 42	Day 56	Day 70	Day 84	Day 98	Day 112
Informed Consent	X								
Follow-up Visits with physical evaluation[a, b,o]	X	X	X	X	X	X	X	X	X
ECOS/WHO Eval	X								
Height/Weight	X								
Concomitant Medications and Treatment	X								
PT/PTT/INR[c]	X								
Hematology[d] and Serum Chemistry[e]	X	X	X		X		X		X
Beta-2-microglobulin and immunoglobulin levels	X								
Blood Sample for heavy water testing		X (on day 1, see [r])	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]
CLL Panel[f]	X								
Bone Marrow Aspiration and Biopsy[g]	X								
Electrocardiogram[h]	X								
CT Scans[i]	X								
Heavy Water (^2H_2O)		X[j,k]	X[k]						

Schedule of Events

Treatment Plan PCI-32765

Evaluation or Procedure	Cycle 1 (weeks 1-4)					Cycle 2 (weeks 6-8)		Cycle 3 through 6 (weeks 10-20)		Cycle 6, 9	Cycle 12	Cycles 13 through 36, and after cycle 36 (see footnote "l")
	Week 1			Week 2	Week 4	Week 6	Week 8	Week10	Week12 16, 20	Week 24, 36	Week 48	
Clinical Assessments	Day 1 (+/-3 days)	Day 3 (+/-1 Day)										
Follow-up Visits' with physical evaluation[a, e, ,l]	X	X		X	X	X	X	X	X	X	X	X
Serum Chemistry[e] and Hematology[d,]	X			X	X	X	X		X		X	X
PT/PTT/INR[p]									X (only week 12)		X	X
Blood Sample for heavy water testing	X	X		X[q]	X[q]	X[q]	X[q]	X[q]	X[q] (only week 12)			
CT Scans[s]									X (only week 12)	X	X	X
PCI-32765 (3 x 140 mg =420 mg)[m]	X	X		X	X	X	X	X	X	X	X	X
Allopurinol 300mg[n]	X	X		X								
Immunoglobulin Levels and Lymphocyte Subpopulation[f]	X								X (only week 12)	X	X	X
Bone marrow aspiration[t]									X (only week 12)	X		X
Blood draw for research testing[u]	X	X			X				X (only week 12)			
Sputum Sample[v]	X											

a. Including vital signs.
b. Patients will be seen at day 1 (+/- 3 days), day 14 (+/- 3 days), and day 28 (+/- 3 days) after beginning ^2H_2O ingestion for follow-up visits with clinical and laboratory assessment, which will include determining if there have been any problems with the ingestion of heavy water and assessment of other adverse events, assessment of concomitant medications, analysis, and discussion of intake logs and blood sampling (60ml) for ^2H_2O kinetic measurements. CBCs (white blood cell, hemoglobin, platelets and differential) will be monitored on days 1, 14, 28 (+/- 3 days), and then every 4 weeks (+/- 3 days) thereafter.
c. Prothrombin Time/PT; Partial Thromboplastin Time/PTT, and International Normalized Ratio/INR.
d. Hematology and serum chemistry: complete blood counts (white blood cell, hemoglobin, platelets and differential) will be monitored on days 1, 14, 28 (+/- 3 days) for the first four weeks and then every four weeks thereafter.
e. Includes sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, and uric acid.
f. IgG, IgM, IgA levels. Flow cytometry assessment for peripheral CLL cells and lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16/56 cells).
g. Prior one month from registration. Bone marrow will be evaluated by flow cytometry for clonality and for *IGHV* mutation studies (unless known), CD38 and ZAP-70 expression, and cytogenetic and genomic abnormalities by FISH
h. Electrocardiogram (prior one month from registration) will be required.
i. CT of the chest, abdomen, and pelvis within 30 days before starting Heavy Water.
j. Patient will be given 50ml 70% heavy water three times a day for the first 5 days (1-5). Patients will be given their first dose in clinic due to the possibility of lightheadedness or dizziness possible effect, and asked to avoid driving or performing potentially hazardous activities for one hour (labeling phase). Patients then will be given individual doses of heavy water to consume at home.
k. Patients will be given individual maintenance doses of 60ml ^2H_2O daily (day 6-28) to be drunk at bedtime. At the end of the 4th week, patients will stop drinking ^2H_2O (washout phase) and be followed for 6-12 weeks until beginning treatment with PCI-32765.
l. After beginning PCI-32765 therapy, patients will be seen for follow-up visits on day +1 (+/- 3 days), day 3 (+/-1 day), day +14 (+/-3 days), day +28 (+/-3 days) and every 2 weeks thereafter for a period of at least equal in duration to that of the initial 2H2O washout phase of 6 to 12 weeks. These visits will include assessment of adverse events and concomitant medications. After that, patients will continue to return to clinic each month (+/- 3 days) or will be seen by a local physician for follow-up visits with clinical and laboratory assessment, including vital signs and physical exam, and laboratory workup, including hematology and clinical chemistry evaluations until the end of 12 cycles. If subjects stay on the study past 12 cycles, they will return for clinic visits for clinical assessment, including vital signs and physical exam, and laboratory workup, including hematology and clinical chemistry evaluations every 3 months (+/- 1 month) for cycles 13 through 36, and every 6 months (+/- 1 month) thereafter. For patients that discontinue therapy with PCI-32765, an end of study visit at MD Anderson will be required. Patients will be followed for at least 2 months (+/- 1 month) after the last dose of PCI-32765 for assessment of adverse events. This will be done in a Leukemia Clinic visit that will be scheduled to occur at 1 month (+/- 10 days) after the last dose of PCI-32765.
m. Administer 3 140mg capsules orally once daily with 8 ounces of water; this will be continued daily. Treatment duration will be 12 cycles, with each cycle consisting of 28 days (336 days total). Treatment beyond cycle 12 is permitted if a patient continuous to demonstrate therapeutic benefit.
n. Allopurinol at the dose of 300mg daily will be given during the first one or two weeks of treatment as standard tumor lysis prophylaxis.
o. Patients are required to be seen at UT MD Anderson Cancer Center for screening period only. The follow-up visits with physical evaluation during weeks 1 through 16 can be done locally at the patient's local doctor's office.
p. PT,PTT,INR, and bleeding time will be monitored after cycles 3 and 12 (+/- 1 week) and if patients stay on the study past 12 cycles, once every 12 cycles (+/- 1 month).
q. Blood draws (60ml) at week 2 (+/- 3 days) and every 2 weeks (+/- 3 days) thereafter for a period of at least equal in duration to that of the initial ^2H_2O washout phase (6 to 12 weeks) for ^2H_2O kinetic measurements. Data obtained from these blood samples will permit a determination of the slope and rate of the appearance of previously labeled CLL cells in the blood, and the slope and rate of the disappearance of labeled cells from the blood.
r. Anti-coagulated blood sample (50ml) and coagulated blood sample (10ml) for baseline ^2H_2O studies on the day of study initiation.
s. CT scans of the chest, abdomen, and pelvis after cycles 3 or 6, and 12. Beyond cycle 12, CT scans are at physicians discretion.
t. Bone marrow will be evaluated by flow cytometry for clonality and for amount of CLL cell infiltration, including detection of minimal residual disease after 3, 6, and 12 cycles (+/- 1 month) of therapy with PCI-32765. Bone marrow testing at later time points is at the treating physician's discretion.
u. Blood draws using one 2.5ml PaxGen tube will be collected in cycle 1, week 1, days 1 (+/- 3 days) and 3 (+/- 1 day), week 4 (+/- 3 days), and week 12 (+/- 3 days), for research testing.
v. One Sputum sample will be collected on day 1 (+/- 3 days) of beginning therapy with PCI-32765 for research testing.