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Protocol Page

A Phase 2 Study of the combination of the Bruton's tyrosine kinase inhibitor PCI-32765 and rituximab in high-risk Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) patients
2011-0785

Core Protocol Information

Short Title	Phase 2 Study of the combination of BTK inhibitor PCI-32765 and rituximab in high-risk CLL and SLL patients
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Full Title:	A Phase 2 Study of the combination of the Bruton's tyrosine kinase inhibitor PCI-32765 and rituximab in high-risk Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) patients
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Terminated 08/09/2018
Version:	12
Submitted by:	Jeannice Y. Theriot--2/21/2018 1:11:29 PM
OPR Action:	Accepted by: Melinda E. Gordon -- 2/23/2018 8:09:19 AM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

Protocol PCI-32765+rituximab 10-22-2012.pdf

Title: A Phase 2 Study of the combination of the Bruton's tyrosine kinase inhibitor PCI-32765 and rituximab in high-risk Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) patients.

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Date of latest update: 10-22-2012 by J. Burger

1.0 Objectives

The primary objective is to assess the activity of the combination of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 and rituximab in patients with high-risk Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL). For this study, we define high-risk CLL as any CLL patient who has a 17p deletion or an 11q deletion or a TP53 mutation. We define high-risk SLL as any SLL patient who has a 17p deletion or an 11q deletion or a TP53 mutation. Alternatively, any patient with a diagnosis of CLL or SLL who had a short remission duration of less than 3 years after prior first-line chemo-immunotherapy would be considered a high-risk CLL or SLL patient, regardless of the presence or absence of any chromosomal marker. The secondary objective is to assess the tolerability of the combination of PCI-32765 and rituximab in CLL/SLL patients.

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 combination of chemo-immunotherapy as initial therapy is associated with high response rates. Unfortunately, once disease relapse has been observed, second line treatment is less effective and response durations are shorter. An alternative to repeating chemo-immunotherapy is to use the monoclonal antibody alemtuzumab. Alemtuzumab is able to induce a response in up to 30% of the patients, but is associated with significant immunosuppression and infections. Also, it lacks activity in patients that have developed bulky lymphadenopathy (larger than 5 centimeters)[1]. Combination of purine-analogue based regimens have limited activity: the combination of fludarabine, cyclophosphamide, rituximab, alemtuzumab (CFAR) is associated with an overall response rate of 65% in patients that have received prior therapy and once patients are fludarabine refractory their median survival is less than twelve months based on our published experience [2].

2.2 High-risk genetic abnormalities (17p deletion, 11q deletion, *TP53* mutation). Standard treatment approaches such as chemo-immunotherapy (e.g., fludarabine/cyclophosphamide/rituximab or FCR) are highly effective in frontline treatment of the majority of CLL patients. However, there is a small, challenging

subgroup of patients whose leukemia is characterized by presence of 17p deletion or *TP53* mutation who respond poorly to chemo-immunotherapy [3, 4] or other treatment modalities for CLL. Related to the poor treatment outcome in this high-risk subgroup, patients with 17p deletion or *TP53* mutation have a short median life expectancy of less than 2 to 3 years [5]. Accordingly, there is an urgent need for alternative therapeutic strategies acting independently of p53 for patients with a 17p deletion or *TP53* mutation, both in the frontline and salvage setting. Because of the poor outcome and responses to standard therapy, patients with 17p deletion or TP53 mutation will not be required to have received prior therapy to enroll.

CLL patients with del(11q22–11q23) represent another challenging clinical subset. This genomic aberration occurs in approximately 20% of patients with advanced CLL. These patients are usually younger than the typical CLL patient (median age: 59 years), and often have extensive lymphadenopathy at the time of diagnosis. The clinical course of patients with the 11q deletion is usually characterized by rapid disease progression with shorter treatment-free survival; a shorter overall survival has been reported in patients younger than 55 years. Although patients with 11q deletion have an improved progression-free survival (PFS) with chemo-immunotherapy, remission duration and overall survival of patients in this subgroup indicate that patients with 11q deletion have an inferior outcome compared with patients with favorable genomic abnormalities[6].

Patients with short remission duration after frontline chemo-immunotherapy, for example with the FCR regimen, constitute another high-risk group of CLL patients[6], and oftentimes such patients also display high-risk cytogenetic abnormalities (del17p, del11q). Such patients typically have low response rates and remission durations when re-treated with chemo-immunotherapy[6].

The preliminary experience with PCI-32765 in relapsed CLL patients with 17p deletion, 11q deletion, or *TP53* mutation indicates that PCI-32765 displays high clinical activity in this risk group. An analysis presented at the 2010 annual meeting of the American Society of Hematology (ASH) showed that single agent treatment with PCI-32765 induces 30% partial remissions (PR, n=3), 30% partial remissions with lymphocytosis (PR with lymphocytosis, n=3), and stable disease in 30% (SD, n=3) of CLL patients with 17p deletion, which is similar to the response rates for CLL patients without 17p deletion. Treatment was discontinuation in only one out of 10 patients with 17p deletion [7]. These data are

based on a relatively short median follow-up time (2 to 8 months), but nonetheless are highly promising and therefore should be verified in a larger cohort of CLL patients. Therefore, to address this unmet medical need and to generate more robust experience with PCI-32765 in high-risk CLL patients, we propose to examine the activity of PCI-32765 and rituximab in 40 CLL patients with high-risk disease features which have relapsed disease.

2.2 PCI-32765

Antigenic stimulation through the B cell antigen receptor (BCR) promotes the expansion of chronic lymphocytic leukemia (CLL) and other malignant B cells [8, 9]. Bruton's tyrosine kinase (Btk), a key component of BCR signaling, can be blocked by PCI-32765, a small-molecule Btk inhibitor, that displayed activity in patients with CLL and other B cell malignancies in the first clinical trial [7]. PCI-32765 is a potent (IC50, 0.5 nM) 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 the enzymatic activity of Btk [10]. Once daily oral dosing results in 24-hour sustained target occupancy. In vitro studies demonstrated that inhibition of Btk in CLL cells results in the blockade of BCR related survival signals, thereby causing apoptosis [11]. Additionally, Dr. Burger's laboratory 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 [11].

A recent analysis of 38 CLL patients from an ongoing Phase Ib/II trial of single-agent PCI-32765 in CLL or SLL included patients with relapsed or refractory disease following at least 2 treatment regimens, and a cohort of patients over 65 years old with treatment naïve disease [7]. When measured clinically and by CT scan every 2 months, patients treated with PCI-32765 typically had an immediate and marked nodal response; 87% of patients 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 patients with 1 CR (8%), 8 PRs (62%) and 2 patients with a nodal response with lymphocytosis (15%). Two additional patients had stable disease. There have been only 3 patients with disease progression, and an additional 3 patients discontinued treatment for reasons other than progressive disease. Of 32 evaluable patients in the Phase Ib study

(with less than 2 months median follow-up) there were 8 PRs (25%) and an additional 17 patients with a nodal response with lymphocytosis. An additional two patients 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 patients).

94% patients experienced an adverse event (AE), 38% patients experienced an adverse event grade 3 or greater in severity (nausea, vomiting, fatigue, diarrhea, headache, rash). The incidence of >/= grade 3 adverse events believed to be related to PCI-32765 was 17%. 14 patients experienced a serious adverse event (SAE), with “serious” defined as requirement for hospitalization. 6 SAE 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) [7]. Two patients in this pooled analysis have died due to progressive disease.

Diarrhea, nausea, and fatigue have been the most commonly reported adverse events, with most of the reported events 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 patients. 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 a) one event of spontaneous subdural hematoma in a patient who took ibuprofen and PCI-32765 at the time of detection of the subdural hematoma, and b) the controversial role of Btk in platelet function and aggregation, we initiated clinical and laboratory assessment of platelet function of patients treated with PCI-32765 on the ongoing Phase I/II trial. There have been no subsequent bleeding events; some patients, however, displayed petechiae or bruises. Therefore, we will implement regular clinical and laboratory assessment and exclude patients with a history of bleeding diathesis or coagulopathy, recent surgical procedure, stroke, or hemorrhage, and patients receiving Coumadin.

2.2 Rituximab

Rituximab is a monoclonal antibody that binds to the human CD20 antigen. Rituximab has been extensively used for the treatment of chronic lymphoproliferative disorders. As a single agent, it is able to induce a response in

up to 30% of the patients with relapsed CLL and is synergistic with chemotherapy agents and other monoclonal antibodies when used in combination[12]. The rationale for combining PCI-32765 with rituximab is to potentiate the clinical efficacy of these agents without increasing their toxicity. This is based on the different mechanisms of action and the non-overlapping toxicity profile. When used as single agent, PCI-32765 typically induces a “compartment shift” of CLL cells from the tissues into the peripheral blood [7]. Clinically, this is associated with a transient surge in lymphocyte counts and lymph node shrinkage during the first weeks of treatment. Because of this lymphocytosis, the patients treated with single agent PCI-32765 often times do not achieve remissions, even though they are asymptomatic and display partial or complete responses at other disease sites. To improve the efficacy of PCI-32765, rituximab is an ideal combination partner, because this antibody is very effective in clearing the blood stream of CLL cells, but less effective at eradicating disease in lymphatic tissues and bone marrow. As such, this protocol combines two agents with complementary single agent activity in different disease sites: PCI-32765 has remarkable activity in the lymphatic tissues, and rituximab is highly effective in clearing the blood stream of CLL cells.

The side effect profile of these two agents also appears to be entirely different and non-overlapping; the toxicity of rituximab consists mainly of infusion reactions, nausea and late transient myelosuppression. PCI-32765 has a very benign side effect profile with low-grade gastrointestinal side effects, no signs of any cumulative toxicity, and no immunosuppression or myelosuppession.

3.0 Study Design

This is a single center open label phase II study to evaluate the efficacy and safety of the combination of PCI-32765 and rituximab in patients with high-risk CLL and SLL who have received prior treatment. Pharmacyclics will supply PCI-32765, commercial supply of rituximab will be used for this study. PCI-32765 will be supplied as capsules containing 140 mg of PCI-32765.

4.0 Treatment Plan

Rituximab (375 mg/m2) will be given intravenously on Day 1, Day 8 (+/- 3 days), Day 15 (+/- 3 days), and Day 22 (+/- 3 days), and then continued once every 4 weeks only on Days 1 (+/- 7 days) during cycles 2 - 6 (+/- 7 days), see Study Calendar, unless patients experience toxicities that warrant early discontinuation

of the rituximab (as determined by the treating physician). There will be no dose modifications of rituximab. PCI-32765 will be started on Day 2 of cycle 1 at a dose of 420 mg (3 x 140-mg capsules) orally once daily with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE due to CYP450 3A4 inhibition) and will be continued daily. There will be no dose modifications of PCI-32765. The doses and schedule of PCI-32765 is based on prior studies with this drug in patients with CLL and other B cell malignancies. At this dose, the target enzyme, Btk, is fully inhibited. The rituximab doses and schedule are considered standard for treatment of CLL patients. A subject diary will be used to aid with PCI-32765 administration compliance. Treatment duration will be 12 cycles, and it will be possible to continue beyond 12 cycles if there is a significant benefit such as an ongoing PR or CR. Response will be evaluated after three, six and twelve cycles. (Each cycle consists of 28 days, see Study Calendar).

Rituximab should be held for any Grade 4 toxicity or for any rituximab-related, clinically significant, unmanageable Grade 3 adverse events. Rituximab should be held until the adverse event returns to baseline or resolves complete. PCI 32765 should be held for any Grade 3 toxicity. PCI-32765 should be held until the adverse event returns to baseline or resolves complete. After Cycle 1, if PCI-32765 is held for > 28 days, the subject should be discontinued from the study.

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. Unused or expired PCI-32765 will be disposed per institutional policy.

Concomitant Medication: Patients receiving Coumadin are ineligible to participate in this study. Patients who recently received Coumadin must be off this medication for at least 7 days prior to start of the study.

PCI-32765 is metabolized by CYP3A4/5 and CYP2D6. Therefore strong inhibitors of CYP3A4/5 and CYP2D6 are prohibited. Once patients are on study they may acquire an illness that requires cocommitant therapy with a drug that inhibits these CYPs. In such cases, 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, for example milder CYP inhibitors.

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.

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.

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.

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**

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted.

5.0 Patient Eligibility

Inclusion Criteria:

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

1. Patients must have a diagnosis of high-risk CLL/SLL and be previously treated with up to 3 lines of prior therapy. High-risk CLL and high-risk SLL is defined by the presence of a 17p deletion or 11q deletion or TP53 mutation. Any CLL and SLL patient who has a short remission duration of less than 3 years after prior first-line chemo-immunotherapy, such as the FCR regimen, also fulfills criteria of high-risk CLL/SLL, regardless of the presence or absence of cytogenetic abnormalities.
2. CLL and SLL patients with 17p deletion or TP53 mutation will not be required to have received any prior therapy, given the poor outcome of CLL/SLL patients to standard frontline chemo-immunotherapy, such patients will be eligible if they are untreated or if they have received up to 3 lines of prior therapy.
3. Patients must have an indication for treatment by 2008 IWCLL Criteria

4. Patients age >/= 18 years at the time of signing informed consent. Understand and voluntarily sign an informed consent. Be able to comply with study procedures and follow-up examinations.
5. ECOG/WHO performance status of 0-1.
6. Patients of childbearing potential must be willing to practice highly effective birth control (e.g., condoms, implants, injectables, combined oral contraceptives, intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as follows: Amenorrhea >/= 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL; a male of childbearing potential is any male that has not been surgically sterilized.
7. Adequate renal and hepatic function as indicated by all of the following: Total bilirubin </=1.5 x institutional Upper Limit of Normal (ULN) except for patients with bilirubin elevation due to Gilbert's disease who will be allowed to participate; an ALT </=2.5 x ULN; and an estimated creatinine clearance (CrCl) of > 30 mL/min, as calculated by the Cockroft- Gault equation unless disease related.
8. 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.
9. A Urine Pregnancy Test (within 7 days of Day 1) is required for women with childbearing potential.

Exclusion Criteria:

1. Pregnant or breast-feeding females
2. Treatment including chemotherapy, chemo-immunotherapy , monoclonal antibody therapy, radiotherapy, high-dose corticosteroid therapy (more than 60 mg Prednisone or equivalent daily), or immunotherapy within 21 days prior to enrollment or concurrent with this trial
3. Investigational agent received within 30 days prior to the first dose of study drug or have previously taken PCI-32765. 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.

4. 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).
5. Patients with uncontrolled Autoimmune Hemolytic Anemia (AIHA) or autoimmune thrombocytopenia (ITP)
6. Patients with severe hematopoietic insufficiency, as defined by an absolute neutrophil count of less than 500/μL and/or a platelet count of less than 30,000/μL at time of screening for this protocol.
7. 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 patient at undue risk to undergo therapy with PCI-32765 and rituximab.
8. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification
9. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc > 470 msec
10. 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.
11. History of stroke or cerebral hemorrhage within 6 months
12. Evidence of bleeding diathesis or coagulopathy
13. 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.
14. Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1. Bone marrow aspiration and/or biopsy are allowed.
15. Serious, non-healing wound, ulcer, or bone fracture.
16. Treatment with Coumadin. Patients who recently received Coumadin must be off Coumadin for at least 7 days prior to start of the study.
17. Any chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), immunotherapy (e.g., alemtuzumab, or ofatumumab),

bone marrow transplant, experimental therapy, or radiotherapy is prohibited during therapy on this study.

18. Use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes (refer to Appendix F) are prohibited within 7 days of starting study drug and during study-drug treatment.
19. Requires treatment with strong CYP3A4/5 and/or CYP2D6 inhibitors.

6.0 Pretreatment evaluation

Pretreatment evaluation will include a physical examination including vital signs, ECOG/WHO performance status, height and weight and recording of concurrent medications (within 7 days of Day 1).

Clinical laboratory evaluation will include serum chemistry. This will include sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, and immunoglobulin levels. Beta-2-microglobulin, coagulation studies (Prothrombin Time/PT; Partial Thromboplastin Time/PTT; and International Normalized Ratio/ INR) within 7 days of Day 1. Hematology: Complete CBC and differential and peripheral blood lymphocyte subset and immunoglobulin levels (within 7 days of of Day 1). Flow cytometry assessment for peripheral CLL cells (CLL panel) and lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD16/56 cells, within 7 days of Day 1).

A Urine Pregnancy Test (within 7 days of Day 1) is required for women with childbearing potential.

Bone marrow aspiration and biopsy within 28 days from of Day 1. Bone marrow will be evaluated by flow cytometry for clonality and for IgVH mutation studies (unless known) ZAP-70 expression (unless known), cytogenetic and genomic abnormalities by FISH. Electrocardiogram (within 28 days from of Day 1). Patients also will undergo CT scans of the chest, abdomen, and pelvis within 2 months from Day 1. Furthermore, patients will be asked to fill out the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) within 7 days of Day 1(Appendix E).

7.0 Evaluation During Study

- Clinic visits (this will include vital signs and physical exam) at The University of Texas, M.D. Anderson Cancer Center are required weekly (+/- 3 days) during the first 4 weeks. Patients for whom weekly visits at MD

Anderson during the first month of therapy cause a major hardship can have their clinic visits and rituximab infusions on day 8 (+/- 3 days), day 15 (+/- 3 days), and day 22 (+/- 3 days) at their local physician's office. Such exceptions must be approved by the treating physician and the principal investigator. Patients return for follow up and then prior to start of cycles 2, 3, 4, 6, 9 and 12 (+/- 1 month). If patients stay on the study past 12 cycles, they return for clinic visits at The University of Texas, M.D. Anderson Cancer Center for clinical assessment (this will include vital signs and physical exam), and laboratory workup (hematology and clinical chemistry) every 3 months (+/- 1 month) for cycles 13 through 36, and every 6 months (+/- 1 month) thereafter, until disease progression or study discontinuation for other reasons.

- Hematology and serum chemistry: complete blood counts (white blood cell, hemoglobin, platelets and differential) will be monitored once weekly for the first four weeks, and then every four weeks thereafter.
- Serum chemistry: basic metabolic profile (sodium, potassium, chloride, CO2, BUN, creatinine and glucose) will be monitored once weekly for the first four weeks and then once every four weeks thereafter until the end of cycle 12. If patients stay on 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, INR will be monitored after 1, 3, 6, and 12 cycles (+/- 1 month) and if patients stay on the study past 12 cycles, once every 12 cycles (+/- 1 month).
- beta-2-microglobulin, lymphocyte subset, immunoglobulin levels, bone marrow aspiration will be performed and evaluated by flow cytometry after 3, 6 and 12 cycles and if patients stay on the study past 12 cycles, once every 12 cycles (+/- 1 month). If patients' bone marrow tests are consistent with a complete remission, no further bone marrow testing is mandatory, and will be ordered at the treating physicians' discretion.
- CT scans of the chest, abdomen, and pelvis after 3 or 6 cycles, and 12 cycles, and once every 12 cycles thereafter. If patients stay on the study past 24 cycles, once every 12 cycles only inpatients with measurable disease, as determined by the treating physician.

- Optional Quality of Life questionnaires (EORTC QLQ-C30) will be collected after 2 weeks, and after cycles 1, 3, 6, and 12. Please refer to plan for monitoring patients in the study calendar for further details.
- Optional correlative laboratory studies will be done before study entry (within 7 days of Day 1), and after 1 week (+/- 3 days), 2 weeks (+/- 3 days), 4 weeks (+/- 3 days), and after cycles 3, 6, and 12, and in patients who fail to respond to therapy at the time of treatment failure (as determined by the treating physician) or at the time of relapse.
- Post Treatment Evaluations: Follow-up evaluations will occur at 60 days (+/- 14 days) following completion of study drug administration. Patients who achieve complete remissions or partial remissions with stable disease and discontinue therapy will be followed long-term every 120 days (+/- 60 days) for up to 5 years or until disease progression or start of a new treatment. The post treatment laboratory evaluations include hematology and serum chemistry with a complete blood counts (white blood cell, hemoglobin, platelets and differential) and a basic metabolic profile (sodium, potassium, chloride, CO2, BUN, creatinine and glucose).

8.0 Criteria for Response

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria will be used [13] (Appendix I). Responses will be assessed after 3, 6 and 12 cycles.

9.0 Evaluation of Toxicity

Adverse events are reported as per UTMDACC and Leukemia Phase 2-3 studies.

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 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 "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". 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.

- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IND Office.

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. 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.

- The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial
- PDMS/CORe will be used as the electronic case report form for this protocol and protocol specific data will be entered into PDMs/CORe.

Adverse Drug Reaction Reporting

AS PER UTMDACC AND LEUKEMIA PHASE II-III STUDIES (APPENDIX C AND APPENDIX D), Toxicity will be scored using CTCAE Version 4.03 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome. Abnormal lab values are only significant if they require intervention or treatment.

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).

10.0 Statistical Design

Endpoint and Design: The primary objective of this phase II study is to assess the activity of the combination of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 and rituximab in Chronic Lymphocytic Leukemia (CLL) in high-risk CLL patients that have received prior therapy. Untreated CLL patients with high-risk disease based on the presence of a 17p deletion or *TP53* mutation will also be eligible. The primary endpoint is progression-free survival (PFS). Denote the median (T) = m_H, for the historical data (H) and m_E, for the experimental (E) trial, where T is time to progression in month. We assume that, T is distributed exponentially with median m_H, with the historical regimen and median m_E, with the new treatment. Under a Bayesian model, we will further assume that m_H, follows an inverse gamma (IG) prior with parameters (18, 85) reflecting the historical data (i.e., 20 patients with chromosome 17 abnormalities who had a median PFS of 5 months)[6], and m_E, follows IG(2.25, 6.25) with the same mean as m_H, but with a much larger variance of 100 to reflect much greater uncertainty about PFS. Progression free survival is defined as the time interval from treatment to progressive disease or death, whichever happens earlier. Patients in complete remission (CR), partial remission (PR) or stable disease (SD) are all counted as progression-free. Due to the characteristic activity of PCI-32765, which typically induces a transient lymphocytosis during the first months of therapy[7], which is not causing any symptoms and which is due to a re-distribution of CLL cells from the tissue compartments (bone marrow, secondary lymphatic tissues) into the peripheral blood, increases in lymphocyte counts can be expected (although in this combination with rituximab are less likely) and will not be considered as a sign of progressive disease.

Interim Analysis on PFS: We will accrue 40 patients and will monitor the PFS continuously, accrual will be terminated early if $Pr(m_H + 2 \text{ months} < m_E \mid \text{data}) <$

0.01. The design operating characteristics based on 1000 simulations are summarized in Table 1. (Accrual of 40 patients with a rate = 3/month, 6 months additional follow-up). For example, the trial will stop early with 97.5% chance (23.3 patients in average) if the median PFS is 3 months, but stop early with 7.8% chance (38.6 patients in average) if the median PFS is 6 months.

Table1. Simulation study with maximum 40 patients:

True median PFS	Pr(stop)	Mean number of patients (25%, 75%)
3 months	0.975	23.3 (14, 33)
4 months	0.632	31.8 (24, 40)
5 months	0.240	36.6 (40, 40)
6 months	0.078	38.6 (40, 40)
7 months	0.038	39.1 (40, 40)
8 months	0.018	39.6 (40, 40)

Interim Analysis on Toxicity: The probability of toxicity (grade 3 or 4) will be monitored based on the Bayesian model (beta-binomial) by assuming a priori probability of toxicity following beta(1,1). The trial will be terminated if Prob(toxicity > 0.25 | data) > 0.90. Following this rule, the trial will be terminated if (# patients with toxicities)/(# patients evaluated) >= 2/3, 3/6, 4/9, 5/12, 6/15, 7/18, 8/22, 9/25, 10/28,11/31, 12/35, 13/38, or 14/40. The operating characteristics for toxicity are summarized in Table 2.

Table 2. Operating characteristics based on 10000 simulation study

True Prob(tox)	Pr(stop early)	Median # Pts (25%, 75%)
0.05	<0.01	40 (40, 40)
0.10	0.04	39 (40, 40)
0.15	0.11	36 (40, 40)
0.25	0.41	28 (9, 40)
0.35	0.79	17 (4, 28)
0.45	0.97	9 (3, 10)
0.55	>0.99	6 (3, 7)

Statistical Analysis: Descriptive statistical analysis will be calculated, including histograms or box-plots, proportions, range, means and standard deviations. A 95% credible interval on response rate will be estimated based on a beta-binomial distribution. Fisher's exact test and Wilcoxon rank test will be used in univariate analyses of categorical (Stage, for example) and continuous variables (Age, for example), respectively. The data analysis will be performed based on the Intent-to-treat. Survival or times to progression functions will be estimated using the Kaplan-Meier method. Toxicity will be reported by type, frequency and severity. Worst toxicity grades per patient will be tabulated for selected adverse events and laboratory measurements. The Department of Biostatistics will provide and maintain a website ("Clinical Trial Conduct") for enrolling patients on this study and evaluating the efficacy monitoring rules described above. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials will be trained in the use of the trial website, with emphasis on the importance of timely updating of follow-up times and recording of events. The monitoring rules described below will be automatically evaluated each time patient data are updated on the trial website. If the stopping rule is met, the study statistician, research nurse, and principal investigator will each receive an email notification that the stopping boundary has been met.

11.0 Amendments, Deviations, Regulatory

Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Pharmacyclics. Amendments should only be submitted to IRB/EC after consideration of Pharmacyclics review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the

reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. Investigators must enter study data into MDACC's PDMS. The Investigator will permit study-related monitoring visits and audits by MDACC's ORERM, Pharmacyclics or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents. The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to MDACC ORERM and the Pharmacyclics representative so that the accuracy and completeness may be checked.

Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards. The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number. Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects. Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines. Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

Study records requirements

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

Premature Discontinuation of Study

The responsible local clinical Investigator, as well as Pharmacyclics, has the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

1. Unsatisfactory enrollment with respect to quantity or quality.
2. Inaccurate or incomplete data collection.
3. Falsification of records.
4. Failure to adhere to the study protocol.

12.0 Optional Correlative Laboratory Studies

Optional correlative laboratory studies will be done before study entry (within 7 days of Day 1), and after 1 week (+/- 3 days), 2 weeks (+/- 3 days), 4 weeks (+/- 3 days), and after cycles 3, 6, and 12. Also, to better understand mechanism of failure to respond to therapy with PCI-32765, samples will be collected and examined in patients who fail to respond to therapy at the time of treatment failure (as determined by the treating physician) or at the time of relapse. The aim of these laboratory studies is to determine changes in CLL cell surface markers, responsiveness of the leukemia cells to B cell receptor stimulation, and plasma chemokine levels. For these studies, two 8 mL tubes of EDTA blood will be collected within 7 days of Day 1, and after 1 week (+/- 3 days), 2 weeks (+/- 3 days), 4 weeks (+/- 3 days), and after cycles 3, 6, and 12. (approximately 1 tablespoon per timepoint). In collaboration with our colleagues from the German Cancer Research Center in Heidelberg (DKFZ Heidelberg, M.D. Anderson sister institution network project) and the Dana-Farber Cancer Institute (DFCI), Boston (Dr. Catherine Wu), we will assay for mutations within the CLL cells in patients responding or not responding to therapy with PCI-32765. For these studies, four 8 mL tubes of EDTA blood (approximately 2 tablespoon per timepoint) will be collected at study entry (within 7 days of Day 1) and at the time of treatment failure (as determined by the treating physician) or at the time of relapse. Also, a sputum sample will be collected during follow-up. Samples collected as part of the optional procedures will be stored at Dr. Burger's laboratory and then sent to the DKFZ and the Dana-Farber Cancer Institute for biomarker testing. Before samples are sent to the DKFZ and the Dana-Farber Cancer Institute, patient names and any personal identifying information will be coded to protect patients' privacy.

Evaluation or Procedure	Screening (30 days)	Screening (14 Days)	Screening (7 Days)	Treatment Plan					If Patient Stays on Study past 12 Cycles		
Clinical Assessments	(Day -30)	(Day -14)	(Day -7 to -1)	Day 7, 14, 21, 28 (+/-3 Days)	Cycle 2, 3, 4, 6, 9, 12 (+/-1 month)	Cycle 1,3,6,12 (+/- 1 month)	Cycles 1,6,12 (+/- 1 month)	Cycles 3,6, 12 (+/- 1 month)	Cycles 13-36 every 3 months (+/- 1 month)	Follow Up After Cycle 36 every 6 months (+/- 1 month)	Once every 12 cycles (+/- 1 month)
Informed Consent			X								
Physical Evaluation[a]			X								
ECOG/WHO Eval			X								
Height/Weight			X								
Concomitant Medications and Treatment			X								
Serum Chemistry[b]			X								
PT/PTT/INR[c]			X								
Hematology[d]			X								
CLL Panel[e]			X								
Bone Marrow Aspiration and biopsy[f]	X										
Electrocardiogram[g]	X										
CT Scans[h]	X							X			
Pregnancy Test			X								
Optional correlative laboratory studies (blood samples)[q]			X	X	X[r]						
Clinical Visits at UT MD Anderson Cancer Center[i]				X	X				X	X	
Hematology and Serum Chemistry[j]				X[k]					X	X	X
PT, PTT, INR						X[l]					X
Beta-2-microglobulin, lymphocyte subset, immunoglobulin levels[m]								X			X

Bone Marrow Aspiration[n]								X			X
CT Scans[o]							X	X			X
Optional Quality of Life Questionanaire[p]						X					
Optional correlative laboratory studies (blood samples)[q]			X	X	X[r]						

a) Includes vital signs (within 7 days of Day 1).

b) Includes sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, and immunoglobulin levels, Beta-2 microglobulin within 7 days of Day 1.

c) Prothrombin Time/PT; Partial Thromboplastin Time/PTT; and International Normalized Ratio/INR within 7 days of Day 1.

d) Complete CBC and differential and peripheral blood lymphocyte subset and immunoglobulin levels (within 7 days of registration).

e) Flow cytometry assessment for peripheral CLL cells and lymphocyte subpopulations (CD3, CD4, CD8, CD19,CD16/56 cells) within 7 days of Day 1.

f) Within one month from registration. Bone marrow will be evaluated by flow cytometry for clonality and for IgVH mutation studies (unless known) ZAP-70 expression (unless known), cytogenetic and genomic abnormalities by FISH.

g) Within one month

h) CT scans of the chest, abdomen and pelvis within two months from Day 1.

i) Includes vital signs and physical exam at The University of Texas MD Anderson Cancer Center during the first 4 weeks, and then after, cycles 2,3,4,6,9 and 12 (+/- 1 month). If patients stay on the study past 12 cycles, they return for clinic visits at UT MD Anderson for clinical assessment and laboratory workup (hematology and clinical chemistry) every 3 months (+/- 1 month) for cycles 13 through 36, and every 6 months (+/1 month) thereafter.

j) Complete blood counts (white blood cell, hemoglobin, platelets and differential) and Serum chemistry: basic metabolic profile (sodium, potassium, chloride, CO2, BUN, creatinine and glucose) will be monitored once weekly for first 4 weeks (+/-3 Days), and then every 4 weeks thereafter. If patients stay on 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.

k) Once every 4 weeks thereafter until the end of cycle 12.

l) PT, PTT, INR will be monitored after 1,3,6 and 12 cycles (+/- 1 month) and if patients stay on study past 12 cycles, once every 12 cycles (+/- 1 month).

m) Will be performed and evaluated by flow cytometry after 3, 6 and 12 cycles (+/- 1 month) and if patients stay on study past 12 cycles, once every 12 cycles (+/- 1 month).

n) If patients' bone marrow tests are consistent with a complete remission, no further bone marrow testing is mandatory, and will be ordered at the treating physicians' direction.

o) CT scans of chest and abdomen after 3 or 6, and 12 cycles (+/- 1 month), and once every 12 cycles thereafter. If patients stay on the study past 24 cycles, once every 12 cycles only inpatients with measurable disease, as determined by the treating physician.

p) Questionnaire collected at baseline, after 3, 6, 12 and every 6 cycles.

q) Optional correlative laboratory studies (blood samples) will be done before study entry, and after weeks 1, 2, 3, 4 (+/- 3 days).

r) Optional correlative laboratory studies(blood samples) at 12 weeks (cycle 3) (+/- 1 month) only and again in patients who fail to respond to therapy after 6 months or at the time of relapse.

Time and Events Schedule: Screening

Evaluation or Procedure	Screening (60 days)	Screening (30 Days)	Screening (14 Days)	Screening (7 Days)
Clinical Assessments	(Day -60)	(Day -30)	(Day -14)	(Day -7 to -1)
Informed Consent				X
Physical Evaluation[a]				X
ECOG/WHO Eval				X
Height/Weight				X
Concomitant Medications and Treatment				X
Serum Chemistry[b]				X
PT/PTT/INR[c]				X
Hematology[d]				X
CLL Panel[e]				X
Bone Marrow Aspiration and biopsy[f]		X		
Electrocardiogram[g]		X		
CT Scans[h]	X			
Pregnancy Test				X
Optional correlative laboratory studies (blood samples)[q]				X

a) Includes vital signs (within 7 days of Day 1).

b) Includes sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, uric acid, and immunoglobulin levels, Beta-2 microglobulin within 7 days of Day 1.

c) Prothrombin Time/PT; Partial Thromboplastin Time/PTT; and International Normalized Ratio/INR within 7 days of Day 1.

d) Complete CBC and differential and peripheral blood lymphocyte subset and immunoglobulin levels (within 7 days of registration).

e) Flow cytometry assessment for peripheral CLL cells and lymphocyte subpopulations (CD3, CD4, CD8, CD19,CD16/56 cells) within 7 days of Day 1.

f) Within one month from registration. Bone marrow will be evaluated by flow cytometry for clonality and for IgVH mutation studies (unless known) ZAP-70 expression (unless known), cytogenetic and genomic abnormalities by FISH.

g) Within one month

h) CT scans of the chest , abdomen and pelvis within two months from Day 1.

i) q) Optional correlative laboratory studies (blood samples) will be done before study entry, and after weeks 1, 2, 3, 4 (+/- 3 days).

Treatment Plan						If Patient Stays on Study past 12 Cycles		
Procedure	Day 7, 14, 21, 28 (+/-3 Days)	Cycle 2, 3, 4, 6, 9, 12 (+/-1 month)	Cycle 1,3,6,12 (+/- 1 month)	Cycles 1,6,12 (+/- 1 month)	Cycles 3,6, 12 (+/- 1 month)	Cycles 13-36 every 3 months (+/- 1 month)	Follow Up After Cycle 36 every 6 months (+/- 1 month)	Once every 12 cycles (+/- 1 month)
Clinical Visits at UT MD Anderson Cancer Center[i]	X	X				X	X	
Hematology and Serum Chemistry[j]	X[k]					X	X	X
PT, PTT, INR			X[l]					X
Beta-2-microglobulin, lymphocyte subset, immunoglobulin levels[m]					X			X
Bone Marrow Aspiration[n]					X			X
CT Scans[o]					X			X
Optional Quality of Life Questionanaire[p]			X					
Optional correlative laboratory studies (blood samples)[q]	X	X[r]						

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