Full Title: Study of Phosphatidylnositol-3-kinase (PI3K) Inhibitor, Idelalisib (GS-1101), in IgM-Associated AL amyloid

Simple Title: Idelalisib for IgM-Associated AL Amyloidosis

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Agent: Phosphotidylinositol-3-kinase (PI3K) Inhibitor Idelalisib (GS-1101); IND #127985

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AMENDMENT THREE: 5/26/16

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OBJECTIVES

1.1.1 Title: Idelalisib for IgM-Associated AL Amyloidosis

1.1.2 Study Design:

This is a single arm, open label study designed to evaluate the safety and efficacy of idelalisib in patients with relapsed IgM-associated AL amyloidosis. Treatment will be comprised of idelalisib at 100mg orally twice daily, with permitted dose modifications for toxicity per manufacturer guidelines (Section 5). The medication will be continued until progression or significant toxicity.

After giving written informed consent, subjects will be evaluated for eligibility for enrollment in the study. Baseline evaluations will be performed as outlined in Section 7. Subjects who satisfy all inclusion and exclusion criteria will begin the study drug. Subjects will be monitored every cycle for safety and hematologic status. Organ function will also be measured during therapy.

Participants will be eligible to continue therapy as long as they do not demonstrate progressive disease or unacceptable toxicity. Standard response criteria for AL amyloidosis hematologic and organ response will be used (Gertz et al. 2010). Hematologic response will also be categorized and reported by Waldenstrom's macroglobulinmia hematologic response criteria. For the purposes of defining progressive disease, the amyloid response criteria will be used. Overall response rate will be measured and participants will be categorized into complete response, very good partial response, partial response and progressive disease. Progression free survival, organ response, safety and tolerability of idelalisib, and quality of life will be assessed.

1.1.3 Patient population: (Specific inclusion and exclusion criteria are detailed in section 3)

1.1.4 Number of sites: 1, Boston Medical Center, 820 Harrison Ave, FGH-2, Boston, MA 02118

1.1.5 Number of patients: 18 patients

1.1.6 Primary Objective:

- To determine the hematologic overall response rate (ORR) in IgM associated AL amyloidosis to a fixed dose of idelalisib. Response rates will categorized into complete response (CR), very good partial response (VGPR), partial response (PR) and progressive disease (PD) according to standard criteria (Gertz et al. 2010).

1.1.7 Secondary Objectives:

- To assess progression free survival (defined as the interval from the first documentation of CR, VGPR or PR to the earlier of the first documentation of disease progression)
- To determine organ response (defined as improvement of involved organ function i.e. eGFR for kidneys, EF for heart etc.)
- To assess the safety and tolerability of idelalisib
- To measure impact on QOL of life using SF-36 assessment tool.

2. BACKGROUND

2.1.1 Study Agent

2.1.1. PI3K Inhibitor Idelalisib

Idelalisib is a potent competitive inhibitor of the ATP binding site of the PI3K p110-delta catalytic domain, which is prominently expressed in cells of hematopoietic origin. Idelalisib is being developed by Gilead Sciences, Inc. as an anti-cancer agent for the treatment of solid and hematologic malignancies. *In vitro*, idelalisib is highly selective for the p110-delta subunit with an IC50 of 2.5 nM. In contrast, the IC50 for the alpha, beta and gamma subunits are 820,

565 and 89 nM, respectively. Idelalisib also showed a greater selectivity for mTOR and other related kinases, but no activity was seen against a panel of >400 diverse kinases (Lannutti 2011). Additionally, in cell-based assays, idelalisib showed a 240- to 2500-fold specificity for p110-delta than for other PI3K class I subunits.

2.1.5. Clinical experience with idelalisib

A total of 25 Phase 1, 2 and 3 clinical studies have been conducted in 300 healthy or non-hematologic subjects and 778 subjects with hematologic malignancies. Eleven studies have been completed in healthy or non-hematologic subjects to study the clinical pharmacology of idelalisib. These studies included phase 1 randomized placebo controlled dose escalation studies in healthy subjects and in subjects with allergic rhinitis, a phase 1 three-period crossover study, a phase 1 comparison study between capsules and tablets, a phase 1 mass balance study, phase 1 studies in patients with hepatic and renal dysfunction, a phase 1 randomized study to evaluate QT/QTc interval, a phase 1 bridging study that included Japanese and Caucasian subjects, a phase 1 to evaluate the effect of idelalisib on probe substrates (patients were on digoxin, midazolam and rosuvastatin), and a phase 1 open label study of idelalisib in combination with GS-9973.

Eight phase 1 and 2 studies have been undertaken in subjects with hematologic malignancies. These include a phase 1 sequential dose-escalation study (101-02), an open-label phase 1 in combination with chemotherapeutic agents and anti-CD20 monoclonal antibody therapy (101-07), a phase 2 study in combination with rituximab in elderly patients with CLL/SLL (101-08), a phase 2 in indolent NHL refractory to rituximab and alkylating agents (101-09), a phase 1/2 in previously treated indolent NHL (101-10), a phase 2 study in relapsed/refractory Hodgkin lymphoma (101-11), a phase 1/2 extension study (101-99) and a phase 2 study of idelalisib in combination with GS-9973 in relapsed/refractory hematologic malignancies (GS-US-339-0103).

In March 2016, decreased overall survival and increased rates of serious adverse events were observed in phase 3 studies evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed iNHL. The excess deaths occurring among idelalisib-treated subjects were generally due to a higher rate of infectious events including sepsis, febrile neutropenia, and opportunistic infections such as Pneumocystis jiroveci (PJP) and cytomegalovirus (CMV). It was concluded that the increased risk of early death may not be outweighed by a reduced hazard of death from disease progression. Gilead conducted a review of its open phase 3 studies in the relapsed CLL setting, and there was no increased risk of death among subjects receiving idelalisib compared to the control groups. It was recommended that studies evaluating idelalisib in first line CLL of iNHL be terminated, and that monitoring inclusive of PJP, CMV and CBC monitoring. It has been further noted that severe hepatotoxicity occurs primarily in younger patients treated with idelalisib in the front line setting, The median time to onset of hepatotoxicity was 28 days.

2.1.6. Summary of Safety Data from Monotherapy Trials

On studies 101-02 (parent) and 101-99 (extension), no DLT was observed during the dose-escalation phase at doses of 50, 100, 200 and 350 mg PO BID, respectively. Therefore, an MTD was not reached. PK data showed no exposure differences between the cohort of patients who received 200 mg PO BID and 350 mg PO BID. Grade 3 or higher LFT elevations that occurred in 28 patients were transient and reversible, and not dose limiting, as they did not recur in 9 of the 14 (64%) patients who were re-challenged with idelalisib. During the 48-week study, the most frequent AEs of any grade were fatigue, diarrhea, pyrexia, nausea, rash, AST increase, cough and ALT increase. SAEs occurred in 44% of patients; the most frequent were pneumonia, febrile neutropenia, diarrhea, pulmonary embolism and acute renal failure. A total of 23 patients (12%) discontinued treatment due to AEs; the most frequent AEs were AST elevation and pneumonia. Twenty subjects (11%) died; 5 due to disease progression, 3 subjects from pneumonia and 12 attributed to fungal pneumonia, PJP, fungal sinusitis, acute respiratory distress, hypoxic respiratory failure, multi-organ failure, cardiac arrest, infection with neutropenia, septic shock and refractory MM. AEs leading to death were reported in 9/20 subjects. Of these, 3 were assessed as possibly related to idelalisib: pneumonia, fungal pneumonia and PJP.

On study 101-09 (indolent NHL), out of 125 participants, 108 and 86 subjects have been exposed to idelalisib 150 mg PO BID for >2 months and >4 months, respectively. Thirty seven percent had reductions to 100 mg PO BID or 75 mg PO BID during the study. Of 125 subjects, 123 (98%) reported an AE. The most frequent were diarrhea, fatigue, cough, neutropenia, nausea and pyrexia. Eighty-three subjects (66%) reported grade 3 or higher AE. The most frequent were neutropenia, diarrhea, increased ALT, pneumonia and increased AST. Twenty-two deaths (18%) were reported; 7 subjects (6%) experienced AES leading to death. AEs leading to death were ARDS, cardiomyopathy with cardiac

arrest, hypoxic respiratory failure and multi-organ failure, pneumonia, septic shock, toxoplasmosis and splenic infarction. Fifty-four patients (43%) experienced SAEs: diarrhea, pyrexia and pneumonia. A total of 19 patients (15%) discontinued the study due to AEs. Diarrhea, ALT and AST elevation, colitis and pneumonitis were the most frequently reported.

On the 101-10 study (low-grade NHL), exposure to drug ranged from 1 day to >6 months with a median of 3.6 months. One subject (9%) died due to GI bleed and sepsis, which the investigator considered not related to study drug. Ten patients (91%) reported at least 1 AE; 5 patients (46%) had grade 3 or higher AEs. Three subjects experienced SAEs from which 2 were assessed as related to study drug (ALT/AST elevation and pneumonitis). Two subjects experienced 1 AE leading to discontinuation (ALT/AST elevation, TLS, sepsis and GI bleed), and 2 subjects experienced AEs leading to dose reduction (ALT increased and colitis). The most frequent AEs were AST increased, ALT increased, diarrhea and fatigue, rash and headache.

In study 101-11 (Hodgkin lymphoma), exposure to drug ranged from 0.5-13.1 months (median 3.3 months). Five subjects (20%) had a dose reduction, and seven (28%) had a dose escalation. Twenty-four subjects (96%) reported at least 1 AE; the most common AEs were fatigue, AST increased, pyrexia, vomiting, ALT increased, chills and cough. Eleven subjects (44%) had at least 1 AE grade 3 or higher: hypoxia, dyspnea and ALT/AST elevation. Eight subjects (32%) experienced at least 1 SAE, which included pneumonia, herpes zoster, skin infection and pyrexia. There was 1 death in a subject who developed hypoxia. The subject had discontinued study drug due to disease progression and had been receiving palliative chemotherapy.

2.1.7. Clinical Pharmacokinetic and Pharmacodynamic Data

After oral administration, idelalisib appears rapidly in plasma. Mean serum half-life range between 6-9 hours. Idelalisib dosed alone over a range of 17-400 mg exhibit less than dose proportional PK. Idelalisib and its major metabolite (GS-563117) are primarily excreted in feces with elimination via urine considered a minor pathway. No clinically relevant food effect was observed on idelalisib PK, thus idelalisib might be given with or without food. Preliminary data indicate no clinically significant differences in idelalisib PK in subjects with hepatic or renal impairment.

Co-administration of idelalisib resulted in higher midazolam systemic exposures (AUC: 5-fold increase; C_{max}: 2.3-fold increase), indicating that idelalisib is a moderate inhibitor of CYP3A. Hence, co-administration of CYP3A substrates with idelalisib might results in an increase in their systemic exposures (e.g. antiarrhythmic agents, calcium channel blockers, benzodiazepines, certain HMG-CoA reductase inhibitors, PDE5 inhibitors and warfarin). Particular caution is recommended with drugs that are highly dependent of CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (e.g. alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole and terfenadine).

Preliminary data indicate that the co-administration of idelalisib and rifampin, a potent inducer of CYP3A, decreases idelalisib exposures by 25%. Co-administration of potent inducers of CYP3A and idelalisib should be avoided (e.g. rifampin, carbamazepine, phenytoin and St. John's wort).

PD evaluations of idelalisib are consistent with the proposed pharmacological anti-tumor effect. Prior to idelalisib dosing, a high level of constitutive pAKT was detected in CLL subjects. Following 8 and 28 days of dosing with idelalisib BID, constitutive phosphorylation of AKT in cells was reduced to the background levels observed in healthy volunteers.

2.1.8. Clinical Efficacy

Idelalisib has shown to be active and well tolerated in a range of B-cell malignancies (Benson 2013; Brown 2013). Idelalisib is highly active as monotherapy in CLL, FL, SLL, LPL, MZL and MCL. Responses to idelalisib are characterized by rapid and durable reductions in lymphadenopathy. Consistently positive results have been demonstrated on a number of endpoints including ORR, DOR and PFS. Idelalisib results thus far support its continued evaluation in subjects with B-cell malignancies. Most of the available clinical efficacy data is based on a dose of 150 mg PO twice daily.

Results from the 101-09 study were recently published (Gopal 2014). In this study, 125 patients with indolent NHL (including 10 patients with WM) who had not had a response to rituximab and an alkylating agent or had had a relapse within 6 months after receipt of those therapies received idelalisib at 150 mg PO BID until disease progression or withdrawal from study. The response rate was 57% with 6% CR rate. The median time to response and DOR were 2 months and 12.5 months, respectively, with a median PFS of 11 months. Based on this study, among the 10 WM patients, 1 PD, 1 SD, 6 MR and 2 PR were observed.

2.1.2 Study Disease and Rationale

AL amyloidosis is a disease where monoclonal light chains form fibrils that deposit in soft tissues and organs leading to multi-organ dysfunction (typically of kidneys, heart and nerves). Historically, treatment strategies for multiple myeloma are used for AL amyloidosis, with high dose melphalan and bortezomib playing prominent roles. In approximately 5% of cases, AL amyloidosis is associated with an IgM paraprotein. These patients have a unique presentation and natural history. Because clonal CD20+ lymphoplasmacytic cells are usually responsible for IgM paraproteins, treatment paradigms based on Waldenstrom's macroglobulinemia (WM) may be more appropriate than myeloma-based strategies. We recently conducted a retrospective chart review of prospectively collected data on 95 patients diagnosed with IgM-related AL amyloidosis at the BUMC Amyloidosis Center from 1996 through 2012. Forty-six of 95 patients who underwent treatment were included in the analysis. Of the 46 treated patients, the highest hematologic response rate was observed with HDM/SCT (5/5: 100%), followed by bortezomib (9/11: 82%), rituximab (12/15: 80%), IMiDs (3/4: 75%) and non-transplant alkylating agents (17/27: 63%).

The relapsing nature of this disease typically requires sequential lines of therapy. There are no prospective trials performed in this patient population, and no standard of care has been identified. Each of the commonly used regimens have toxicities that are particularly undesirable in amyloid patients. For instance, steroids cause worsening fluid retention and volume status problems in patients already struggling with hypoalbuminemia, heart failure and renal insufficiency. Bortezomib can exaggerate peripheral neuropathy which is very common in AL patients. An effective, steroid-free regimen that does not cause neuropathy would be a major step forward for this field.

Idelalisib, an oral inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3K), has been shown to be active and well tolerated in patients with relapsed/refractory non-Hodgkin lymphoma including chronic lymphocytic lymphoma, and lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia (WM). The side effect profile of idelalisib merges well with the known predisposition to toxicity of amyloidosis patient. The response rates reported for idelalisib in WM compare favorably with the response rates for IgM-associated AL patients reported in retrospective series. Response rates are likely most favorable in patients with $MYD88^{L265P}$ or $CXCR4^{WHIM}$ *mutations*[T]

3. PARTICIPANT SELECTION

3.1.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 IgM paraprotein identified on serum immunofixation electrophoresis OR light chain-restricted CD20+ lymphoplasmacytic population on biopsy of bone marrow or lymph node (identified by H&E/immunohistochemistry or flow cytometry) OR positive myeloid differentiation primary response gene 88 (MYD88-L265P) OR $CXCR4^{WHIM}$ mutation on submitted samples

3.1.2 Biopsy-proven, relapsed or refractory AL amyloidosis

3.1.3 Age $\geq$ 18 years

3.1.4 ECOG performance status $\leq$2 (see Appendix A.)

3.1.5 Difference between serum free light chains (FLC) of >30 mg/L or quantifiable IgM paraprotein >0.5 g/L

3.1.6 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count $\geq$ 1,000/mm^3
- Platelets $\geq$ 50,000/mm^3

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

3.1.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Previous treatment with idelalisib

3.2.2 GFR <15 ml/min

3.2.3 Cardiac biomarker Stage III disease as determined by BNP >100 pg/mL and Troponin-I >0.1 ng/mL (Girnius 2014)

3.2.4 ALT/AST values >2.5x ULN, Bilirubin >1.5 x ULN

3.2.5 CNS malignancy or other active malignancy

3.2.6 Lactating or pregnant women

3.2.7 Exposure to another investigational drug within 4 weeks prior to start of study treatment

3.2.8 Ongoing alcohol or drug addiction as determined by investigator

3.2.9 Amyloid-directed therapy within the past 28 days

3.2.10 History of Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV) (assessed by positive Hep B PCR or HepB Surface Antigen), and/or Hepatitis C Virus (HCV) infection

3.2.11 t(11,14) translocation identified on bone marrow cytogenetics or by FISH

3.2.12 Known lytic bone lesions

3.2.13 Positive CMV PCR

3.2.14 Previously untreated AL amyloidosis (newly diagnosed)

3.2.15 Unwilling or unable to comply with the protocol

4. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for idelalisib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

4.1.1 Agent Administration

4.1.1 Idelalisib

Idelalisib will be administered orally at a dose of 100 mg (one tablet) twice daily. At 3 month visit, if the patient has no toxicities grade 2 or greater that are attributable to idelalisib, dose escalation to 150 mg PO BID is allowed at investigator discretion. Participants will be treated until progression, unacceptable toxicity, or decision to withdraw from the trial. Dose reductions due to toxicity will be permitted, according to dose modification instructions (Section 5).

The study drug idelalisib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. Participants will be instructed to take the study drug at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the patient should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit; this must be documented in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

Drug accountability will be done at each study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. A new prescription for either one cycle or three cycles, will be filled by the participant.

Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label.

Idelalisib will be provided by Gilead Sciences, Inc. Idelalisib is formulated as tablets for oral administration and will be available for this study in 150-mg tablets or 100-mg tablets.

4.1.2 General Concomitant Medication and Supportive Care Guidelines

Participants will be required to take antibiotics for prevention of *Pneumocystis jiroveci* infection throughout the duration of the clinical trial. Participants will be instructed to take 1 tablet of Bactrim DS every Monday, Wednesday and Friday while taking idelalisib. If there is a concern for allergy or other adverse reaction to Bactrim DS in the opinion of the treating investigator, atovaquone 1500 mg daily may be prescribed instead.

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted. All concomitant medications/significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded. The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No anticancer agents other than the study medication should be given to participants. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (e.g. G-CSF, erythropoietin, platelet growth factors etc.) are not to be administered prophylactically but may be prescribed at the discretion of the treating physician for treatment related hematologic events in accordance with ASCO guidelines.
- Concurrent administration of idelalisib and strong CYP3A4/5 inhibitors (such as clarithromycin, ketoconazole, itraconazole, and ritonavir) and inducers (such as rifampin and rifabutin) should be avoided. Alternatives should be sought if possible. Provided there is no alternative treatment available, the Principal Investigator should be consulted, and treatment should be administered with caution; patients should be closely monitored for potential toxicities with temporary interruption of idelalisib. Examples are provided in Table 4-1.
- Concurrent administration of idelalisib and moderate CYP3A4/5 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4/5 inducers (such as carbamazepine and phenobarbital) should also be avoided if possible, or after consulting with the Principal Investigator, used with caution with increased frequency of safety monitoring and temporary interruption of idelalisib
- Competitive inhibition could occur when idelalisib is combined with drugs, which are also CYP3A4/5 substrates; and therefore should be avoided.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used with caution with increased frequency of safety monitoring and temporary interruption of idelalisib.
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.

- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No green tea or foods/supplements containing green tea or extract.
- No chronic treatment with systemic steroids (at dosages equivalent to prednisone >20 mg/day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

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

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalized in the list below.
- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

Table 4-1 Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
TELITHROMYCIN	Pioglitazone
Moderate inhibitors:	Rifabutin
Aprepitant	Rifampin
erythromycin	St. John's Wort
Diltiazem	Troglitazone
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
chloramphenicol	
Boceprevir	
ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
mifepristone	
Norfloxacin	
norfluoxetine	
star fruit	
Telaprevir	
troleandomycin	
voriconazole	

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

4.1.3 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression (including initiation of new therapy) or death
- Dose delay of >28 days for toxicity
- Intercurrent illness that prevents further administration of treatment
- Unacceptable toxicity or adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants who meet criteria for disease progression but are deemed by the investigator to be clinically benefiting from idelalisib will be permitted to continue on protocol at the Principal Investigator's discretion. Clinical benefit is determined by considering clinical data, such as overall participant performance and disposition, CBC, and when necessary, bone marrow biopsy results and CT scans.

4.1.4 Duration of Participation

Participants will continue to take Idelalisib per-protocol until disease progression or unacceptable adverse event. Study visits will occur two weeks after starting Idelalisib, then monthly from the start of Idelalisib for three months, followed by every three months from the start of Idelalisib thereafter until disease progression or the start of another line of therapy, whichever occurs first. For patients who have responded but come off Idelalisib for reasons other than progression, they will be followed every 6 months until progression or another line of therapy. An end of study visit will take place 30 days following the last dose of Idelalisib. The duration for individuals, and duration of the study, are dependent upon disease response. We anticipate no more than 2 years duration for individual subjects. We anticipate the study will remain active for a total of 4 years including enrollment, treatment, follow-up and data analysis.

5. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. If administration of idelalisib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to the manufacturer's guidelines seen below. Toxicities requiring dose modification that recur upon restarting drug should be discussed with the principal investigator.

Dose Modifications for Toxicities Due to Idelalisib			
Pneumonitis: Discontinue Idelalisib in patients with any severity of symptomatic pneumonitis **Intestinal Perforation**: Discontinue Idelalisib **Positive CMV PCR**: Consider confirmation (at investigator discretion) Discontinue Idelalisib			
ALT/AST	**>3-5 x ULN**	**>5-10 x ULN**	**>10 x ULN**
	Maintain Idelalisib dose. Monitor at least weekly until <1 x ULN.	Withhold Idelalisib. Monitor at least weekly until ALT/AST are <1 x ULN, then may resume Idelalisib at 100 mg BID (or if taking 150mg BID, decrease to 100mg.	Discontinue Idelalisib permanently.

Bilirubin	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**
	Maintain Idelalisib dose. Monitor at least weekly until <1 x ULN.	Withhold Idelalisib. Monitor at least weekly until bilirubin is <1 x ULN, then may resume Idelalisib at 100 mg BID (or if taking 150mg BID, decrease to 100mg).	Discontinue Idelalisib permanently.
Diarrhea	**Moderate diarrhea** (increase of 4-6 stools/day over baseline)	**Severe diarrhea or Hospitalization** (increase of 7 or more stools/day over baseline)	**Life-threatening diarrhea**
	Maintain Idelalisib dose. Monitor at least weekly until resolved.	Withhold Idelalisib. Monitor at least weekly until resolved, then may resume Idelalisib at 100 mg BID (or if taking 150mg BID, decrease to 100mg).	Discontinue Idelalisib permanently.
Neutropenia	**ANC 1.0 to <1.5 Gi/L**	**ANC 0.5 to <1.0 Gi/L**	**ANC <0.5 Gi/L**
	Maintain Idelalisib dose.	Maintain Idelalisib dose. Monitor ANC at least weekly.	Interrupt Idelalisib. Monitor ANC at least weekly until ANC ≥0.5 Gi/L, then may resume Idelalisib at 100 mg BID (or if taking 150mg BID, decrease to 100mg).
Thrombocytopenia	**Platelets 50 to <75 Gi/L**	**Platelets 25 to <50 Gi/L**	**Platelets <25 Gi/L**
	Maintain Idelalisib dose.	Maintain Idelalisib dose. Monitor platelet counts at least weekly.	Interrupt Idelalisib. Monitor platelet count at least weekly. May resume Idelalisib at 100 mg BID (or if taking 150mg BID, decrease to 100mg) when platelets ≥25 Gi/L.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANC, absolute neutrophil count; BID, twice daily; ULN, upper limit of normal			

Dose re-escalations will not be permitted once dose reduced to next lower dose level. If a participant requires a dose delay of 28 days or more, then the participant must be discontinued from the study.

5.1.1 Toxicity Management

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to idelalisib will be followed until the adverse event or abnormal laboratory resolves or returns to grade 1. If a participant requires a dose delay of 28 days or longer, then the participant must be discontinued from the study. All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each participant completed the clinical study. The reason either study treatment or observations were discontinued will be recorded. Reasons that a participant may discontinue participation in a clinical study are considered to constitute one of the following:

1. Adverse event(s)
2. Abnormal laboratory value(s)
3. Abnormal test procedure result(s)
4. Disease progression (including initiation of new therapy)
5. Protocol violation
6. Participant withdrew consent
7. Lost to follow-up
8. Administrative problems (including study-related issues, IRB and other regulatory issues, and drug administration issues)
9. Death
10. General or specific changes in the participant's condition that render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants who meet any criteria 1-4 above but are deemed by the investigator to be clinically benefiting from idelalisib (i.e. remain asymptomatic or IgM levels not increasing further) will be permitted to continue on protocol at the Principal Investigator's discretion. Clinical benefit is determined by considering clinical data, such as overall participant performance and disposition, CBC, and when necessary, bone marrow biopsy results and CT scans.

6. DRUG FORMULATION AND ADMINISTRATION

6.1 Idelalisib

6.1.1 Idelalisib Formulation

Idelalisib is provided as plain-faced or debossed, modified oval tablets. The 100-mg tablets are orange film-coated and the 150-mg tablets are pink film-coated. The debossed 100-mg tablets have "GSI" on one side and "100" on the other. The 150-mg tablets have "GSI" on one side and "150" on the other.

6.1.2 Idelalisib Package, Storage and Handling

Idelalisib tablets are packaged in white, high-density polyethylene bottles with a polyester fiber coil and are closed by a polypropylene, child resistant induction-sealed cap. Bottles contain 60 tablets.

Measures that minimize drug contact with the body should always be considered during handling, preparation and disposal procedures. Any unused drug should be disposed of in accordance with local requirements.

Idelalisib tablets should be stored at a controlled room temperature between 20-30^{o}C (68-86^{o}F), with excursions permitted from 15^{o}C (59^{o}F) to 30^{o}C (86^{o}F). Brief excursion (less than 1 week) to temperatures as low as -10^{o}C or as high as 40^{o}C will not adversely affect the drug.

6.1.3 Idelalisib Availability

Idelalisib is commercially available, but will be supplied free-of-charge from Gilead Sciences, Inc. Drug will be shipped to BMC by Gilead Sciences, Inc., with standard commercial labeling. As study visits are every three months, a three month supply of Idelalisib will be provided at each visit.

6.1.4 Idelalisib Administration

Idelalisib should be self-administered daily by the participant and should be taken at approximately the same time each day. Idelalisib should be administered orally twice daily with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE due to CYP450 3A4 inhibition). The tablets should be swallowed intact and participants should not attempt to dissolve tablets in water. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the participant should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Dietary habits around the time of idelalisib intake should be as consistent as possible throughout the study. If the pills are vomited this should be noted on the diary, but a replacement dose should not be taken that day. A study diary will be used to aid with study drug administration compliance.

At each study visit, enough idelalisib will be dispensed until the next cycle. For visits occurring monthly, one cycle worth of pills will be dispensed. For visits occurring every 3 months, three cycles' worth of pills will be dispensed.

6.1.5 Idelalisib Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

6.1.6 Idelalisib Destruction and Return

Unused idelalisib tablets will be returned by the participant, collected and counted at each study visit, and will be destroyed per institutional policy. Destruction will be documented in the Drug Accountability Record Form.

6.2 Bactrim DS

6.2.1 How Supplied

BACTRIM™ DS (double strength) is commercially available as TABLETS (white, oval shaped, scored) containing 160 mg trimethoprim and 800 mg sulfamethoxazole – bottles of 100 (NDC 49708-146-01). Imprint on tablets (debossed): (front) BACTRIM DS. Please refer to the agent's package insert for additional information.

6.2.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F). DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER

6.2.3 Toxicity

- Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia.
- Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.
- Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.
- Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.
- Metabolic and Nutritional: Hyperkalemia, hyponatremia.
- Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.
- Psychiatric: Hallucinations, depression, apathy, nervousness.
- Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.
- Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with BACTRIM, mainly in AIDS patients.
- Respiratory: Cough, shortness of breath and pulmonary infiltrates.
- Miscellaneous: Weakness, fatigue, insomnia.

6.2.4 Administration

BACTRIM DS should be self-administered by the participant every Monday, Wednesday and Friday while taking idelalisib. Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

At each study visit, compliance will be assessed.

7.0 STUDY CALENDAR

	At enrollment	Every 2 weeks for 3-6 months after starting Idelalisib[3-5]	One and two months after starting Idelalisib[3]	Monthly while taking Idelalisib	Every three Months[6]	End of Study Treatment Visit[7]
PHYSICAL						
History & Physical Exam	X				X	X
Height & Weight	X					
ECOG Performance Status (see Appendix A)	X		X		X	X
Adverse Event Monitoring			X		X	X
SF-36 (QOL)	X		X		X	
LABORATORY-Serum						
Complete Blood Count with Differential	X	X[4]	X		X	X
Beta-HCG[1]	X					
Chemistry including: BUN, creatinine, glucose, sodium, potassium, chloride, bicarb, cholesterol, CK, calcium, total protein, LDH, magnesium, phosphorous, triglycerides, uric acid, TSH, amylase	X		X		X	X
BUN / Serum Creatinine	X		X		X	X
Hepatic Function Testing: ALT/AST, Bilirubin, Albumin, Alkaline Phosphatase	X	X[5]	X		X	X
β-2 Microglobulin / C-reactive protein	X		X		X	
Cardiac enzymes: BNP/ Troponin I	X		X		X	
Serum free light chain assay	X		X		X	
SPEP, SIFE, Immunoglobulins	X		X		X	
Vitamin B12, folate, ESR, retic %	X		X			
Coagulation profile: PTT, INR, D-dimer, Factor X	X		X		X	
Hepatitis Serologies: Hep B Surface Antigen, Hep B Core antibody, Hep C Antibody	X					
HIV antibody- 1+2	X					
CMV PCR	X			X		
1, 3 β-D-glucan	X			X		
LABORATORY-Urine						
Urinalysis	X				X	
24 hour urine: total protein, creatinine, kappa, and lambda	X				Every 6 months	
UPEP / UIFE / TV	X				X	
PATHOLOGY						
BM biopsy w/ MYD88 and CXCR4^{WHIM} analysis[2]	X					
FISH for t(11;14)	X					
Fat aspirate (if not previously done)	X					
X-RAYS AND SCANS						
ECG / CXR	X					
Echocardiogram	X				Every 6 months	
PFTs	X					

[1]For women of childbearing potential only: Serum pregnancy test is required at screening.
[2]If bone marrow biopsy and aspiration must have been repeated following any previous therapy > 1 cycle.
[3] These visits including physical exam and blood work may performed by local physician and confirmed by telephone contact if patient unable to return for week 2 visit or monthly visits on months 1 and 2.
[4]CBC with differential should be monitored every 2 weeks for the first 6 months of treatment
[5]Hepatic function tests should be checked every 2 weeks for the first 3 months of treatment
[6]While on study drug or until disease progression or start of another therapy.
[7]30 days following last dose (+/-) 7 days.

8. MEASUREMENT OF EFFECT

8.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

8.2 AL Amyloidosis Hematologic Response Criteria

CATEGORY	RESPONSE CRITERIA
Complete response (CR)	• Normal serum free light chain ratio • Negative serum and urine immunofixation electrophoresis
Very good partial response (VGPR)	• Difference in serum free light chains less than 40 mg/L
Partial Response (PR)	• >50% Reduction in the difference in serum free light chains
Stable Disease (SD)	• Meets neither criteria for CR, VGPR, PR or PD
Progressive Disease (PD)	• From CR, an increase in serum M-protein to > 0.5 g/dL, an increase in the urine M-protein to > 200 mg/day, or an increase in the serum monoclonal free light chain by > 10 mg/dL (100 mg/L). From VGPR, PR or SD, an increase in the serum M-protein from the lowest level by > 50%, as long as the absolute magnitude of this increase is > 0.5 g/dL; or an increase in the urine M-protein from the lowest level by 50%, as long as the absolute magnitude of this increase is > 200 mg/day; or an increase in the serum or urine monoclonal free light chain by > 50% from the lowest level, as long as the absolute magnitude is > 10 mg/dL (100 mg/L).

8.3 Waldenstrom's Macroglobulinemia Hematologic Response Criteria

CATEGORY	RESPONSE CRITERIA
Complete response (CR)	• Serum IgM values in normal range • Disappearance of monoclonal protein by immunofixation
Very good partial response (VGPR)	• Monoclonal IgM protein is detectable • At least 90% reduction of serum IgM from baseline or serum IgM values in normal range
Partial Response (PR)	• Monoclonal IgM protein is detectable • At least 50% but <90% reduction of serum IgM from baseline
Minor Response (MR)	• Monoclonal IgM protein is detectable • At least 25% but <50% reduction of serum IgM from baseline
Stable disease (SD)	• Monoclonal IgM protein is detectable • <25% reduction and <25% increase in serum IgM from baseline
Progressive disease (PD)	• ≥25% increase in serum IgM with a total increase of at least 500 mg/dL from nadir[1] o Reconfirmation of initial IgM increase is required when IgM is sole criterion for PD confirmation.
1. Nadir is defined as the lowest serum IgM value obtained at any time from baseline onwards with the exception that serum IgM levels post-plasmapheresis will not be considered for up to 6 weeks.	

8.4 Organ Response Criteria

A subject will be said to have had an organ response in an involved organ if any of the following criteria are met.

- Kidney: 50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency (defined as a 25% increase in serum creatinine, as long as that is > to an absolute increase of 0.5 mg/dL). In the case of nephrotic syndrome: a decrease in proteinuria to < 1g/24h and an improvement in one of 2 extrarenal features – normalization of serum albumin or resolution of edema and/or discontinuation of diuretics in response to improvement in edema.
- Heart: ≥ 2 mm reduction in the interventricular septal (IVS) thickness by echocardiogram, improvement of ejection fraction by ≥ 20% (echocardiogram must be performed at the same institution), or decrease in 2 NYHA classes without increase in diuretic need.
- Liver: ≥ 50% decrease in normalization of an initially elevated alkaline phosphatase level or reduction in the size of the liver by at least 3 cm if assessed by imaging.
- Neuropathy: While neurotoxicity is acceptable for determining organ involvement, it will not be adequate for assessing organ response; organ response will be indeterminable for subjects in which neurotoxicity is the only site of organ involvement.
- Gastrointestinal Tract: While GI involvement is acceptable for determining organ involvement, it will not be adequate for assessing organ response: organ response will be indeterminable for subjects in which GI is the only site of organ involvement.

8.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death). Follow-up will continue until disease progression, which we anticipate to be no more than 2 years.

8.6 Quality of Life

Quality of Life (QOL) score on the SF-36 survey will be measured at the start of each cycle for each patient and results for the entire patient group will be provided in a descriptive fashion without formal statistical analysis

9. ADVERSE EVENTS

9.1 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):
• Results in death
• Is life-threatening[1]
• Requires in-patient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability or incapacity[2]
• Is a congenital anomaly or birth defect
• Is an important medical event[3]
• Suspected positive Pregnancy[4]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important
[4] The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 9.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

Unexpected fatal or life-threatening and related experiences associated with the use of the study treatment will be reported to Gilead Sciences within three business days of awareness of the event. All other serious experiences (regardless of expectedness) associated with the use of the study treatment will be reported to Gilead Sciences within seven business days of awareness of the event.

The Investigator must submit each IND safety report in a narrative format or on FDA Form 3500A to the company at the Gilead Sciences Drug Safety department:

Gilead Sciences Drug Safety & Public Health	
Address:	333 Lakeside Dr, Foster City, CA 94404
US Local Fax:	650-522-5477
US Local Phone:	650-522-5114
E-mail	Safety_FC@gilead.com

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

9.2 Adverse Drug Reaction Reporting

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 subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject'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 subject's outcome.

AEs and SAEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent therapy for amyloidosis, whichever occurs first. All SAEs should continue to be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.3 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of Grade 2 or higher AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10. DATA MANAGEMENT

10.1 Analyses and Reporting

Data will be analyzed and reported after study is completed or meaningful endpoints are reached. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

10.2 Data Monitoring Committee

Toxicity and accrual monitoring will be performed on a routine basis by the study investigators as well as the multidisciplinary members of the Amyloid Center at Boston University, which has over 40 years' experience in the treatment of AL amyloidosis. Subjects will undergo toxicity assessment, performance status assessment and laboratory tests according to the study calendar in Section 7. Organ response assessment will be conducted every six cycles. The clinical status and laboratory reports of the study participants will be reviewed routinely by the co-investigators at the weekly meetings of the Amyloid Program. Dose modifications/interruptions or discontinuation will be implemented according to Section 5.

In addition, the BMC Cancer Center's Internal Data and Safety Monitoring Committee (DSMC) will review the protocol, and will determine review frequency based on level of risk. The protocol will be reviewed at least annually by the DSMC. Please see full DSMB Charter in Appendix B.

10.3 Study monitoring and auditing

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 onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Gilead 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.

11.0 REGULATORY CONSIDERATIONS

11.1 Protocol Amendments

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

11.2 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 in writing of such deviation from protocol. Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

11.3 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.

11.4 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.

11.5 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; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and 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.

12.0 STATISTICAL CONSIDERATIONS

This is a single arm, open label study designed to evaluate the safety and efficacy of idelalisib in IgM-associated AL amyloid patients. Patients will receive treatment until progression or unacceptable toxicity. Treatment will be comprised of idelalisib at 100 mg orally twice daily.

12.1 Study Design/Endpoints

The primary endpoint of the current study is:

- To assess the hematologic overall response rate (ORR) of idelalisib in IgM-associated AL amyloid patients.

The secondary endpoints are:

- To assess the safety and tolerability of idelalisib
- To evaluate organ response
- To evaluate progression free survival
- To measure impact of idelalisib treatment on quality of life

12.2 Sample Size/Accrual Rate

We assume a total of 6 patients per year for 4 years meeting inclusion/exclusion criteria, with approximately 60% enrollment for a total of 15 patients. Using an optimal 2-stage design, we assume α=.05, p_0 = .05 and p_1 = .25, where p_0 and p_1 are the response probabilities under the null and alternative hypotheses, respectively. Then we would have 80% power to detect a statistically significant response rate with 9 patients enrolled in Stage 1, proceeding to 9 patients enrolled in Stage 2 only if at least one patient has a response during the first stage. Using this design the intervention would be declared successful if at least a total of 3 responses are observed during the study period.

12.3 Stratification Factors

No stratification factors will be applied to any analysis.

12.4 Reporting and Exclusions

All participants who met the eligibility criteria and were enrolled in the trial will be included in the main analysis of the response rate. All conclusions will be based on all eligible participants.

13.0 REFERENCES

Benson DM, Kahl BS, Furman RR, et al. Final results of a phase I study of idelalisib, a selective inhibitor of PI3K{delta}, in patients with relapsed or refractory indolent non-Hodgkin lymphoma (iNHL). *ASCO MEETING ABSTRACTS* Jun 17, 2013: 8526.

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Gertz et al. 2010) Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): A consensus opinion from the 10th International Symposium on amyloid and amyloidosis. Am J Hematol 2005; 79(4):319-28.

Girnius S, Seldin DC, Meier-Ewert HK, et al. Safety and efficacy of high-dose melphalan and auto-SCT in patients with AL amyloidosis and cardiac involvement. Bone Marrow Transplantation 2014; 49(3): 434-9.

Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. N Engl J Med 2014; 370:1008-18.

Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110-delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood 2011; 117(2): 591-4.

14.0 APPENDICES

14.1 APPENDIX A: Performance Status Criteria

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

14.2 APPENDIX B: Cancer Research Center Data Safety Monitoring Charter

Cancer Research Center Data Safety Monitoring Charter

Data Safety and Monitoring Program
BU/BMC Cancer Center
Boston, MA 02118
617-638-8265

Table of Contents:

Mission:
The Cancer Center Data Safety Monitoring Committee (DSMC) functions to ensure the safety of participants in investigator-initiated, interventional clinical trials conducted by BUMC Cancer Center members by monitoring clinical trial progress and the collection, validity and integrity of the data collected on clinical trials under its jurisdiction. The committee ensures compliance with FDA, NCI and IRB requirements. The policies and procedures of the Data and Safety Monitoring Committee follow NCI guidelines.

Background:
All cancer related interventional protocols from any department must be reviewed by the Cancer Center Scientific Review Committee (SRC). This includes trials that are recruiting individuals to cancer prevention or detection; treatment of disease or symptoms; and studies of cancer survivors, i.e. people who have had a previous diagnosis of cancer.

At the time it approves a new investigator-initiated, interventional protocol, the SRC assigns a category of risk that determines the level of monitoring required by the DSMC**.** The level of risk (low, moderate high) is based on a number of criteria, including the expected duration of the study based on the study design and a realistic estimate of the rate of enrollment; the nature of the study population (*e.g.,* prisoners, pregnant women); procedures to ensure the safety of subjects in accordance with the degree of risk; the complexity of methods needed to ensure the validity and integrity of the data; and planned data management systems including case report forms, records and the plan for data collection. Multiple-site studies must also have an operational plan that describes the procedures for reporting serious adverse events to the Cancer Clinical Trials Program (CCTP), IRB, FDA, and NIH, as appropriate, and plans for notifying participants of trial results and communicating relevant study information to participants' health providers (*e.g.,* cessation of drugs, changes in dosage, *etc*.)

Prior to implementation, all studies in need of internal monitoring must have a monitoring plan approved by the SRC, including frequency of reviews based on the level of risk and accrual target. Typically, high-risk studies are reviewed quarterly by the DSMC, moderate risk studies are reviewed twice each year, and low risk studies are reviewed annually. However, each study is considered independently. Implementation of monitoring plans approved by the SRC is the responsibility of the DSMC. The DSMC Coordinator manages the logistics associated with DSMC sessions.

Two months prior to a scheduled DSMC review, the PRMS Administrator informs the principal investigator and primary study coordinator of the upcoming review. At this time, the research staff is requested to submit a completed DSMC Report Form (Appendix I) and associated documents to the PRMS Administrator (for each DSMC review).

In addition to being monitored by the DSMC, clinical studies also undergo annual auditing by the SRC (see below). Two months prior to an annual DSMC review, the PRMS Administrator informs the Principal Investigator and primary study coordinator to prepare protocol documents for audit and informs the PRMS Audit Committee that an audit is

due. The Audit Committee audits 10% of charts for a given year, or a minimum of three charts, to assess fidelity to the approved protocol, study documentation, timeliness of adverse reporting, accuracy of data collection, and other variables. The audit report, which lists all major and lesser deviations from protocol, is submitted to the Principal Investigator and to the DSMC.

One month prior to the DSMC Meeting, the PRMS Administrator distributes pertinent documents to the Committee members, including.

- Completed DSMC Form (Appendix I)
- Electronic copy of the protocol
- Spreadsheet including: date of enrollment, patient initials, patient number, gender, age, race, status on study (*i.e.*, active, follow-up, completed, expired)
- A copy of the Data Safety Monitoring Plan outlined in the INSPIR application.
- SAE reports, follow-up reports, and outcome reports
- Audit Committee Report (if annual review)

Responsibilities of the DSMC

< Familiarize themselves with the research protocol(s) and review proposed plans for data safety monitoring, and protocol data submitted by the research staff.

< Review annual audit report from the PRMS Audit Committee to evaluate the appropriateness of the conduct of the study.

< When applicable, review interim analyses of toxicity data prepared by the study statistician according to the data safety monitoring plan and upon special request. Recommendations regarding study modification, or termination of study accrual based on these analyses can be made at that time by the DSMC. Modifications may include dropping a treatment arm based on toxicity results, dose adjustment, increasing or decreasing sample size, *etc.*

< Provide the PI and the Cancer Center Scientific Review Committee with a written report following each DSMC meeting summarizing its review of the trial as related to the cumulative toxicities observed and any relevant recommendations related to continuing, amending or terminating accrual to the trial.

< The Committee has the authority to require amendments, to recommend suspension or termination of any research activities that fall under its jurisdiction, and to institute other requirements to improve participant safety

< Confidentiality Procedures: No communication of the deliberations or recommendations of the DSMC is allowed outside the DSMC, except as provided for in the DSM policy. It is also understood that industry studies are considered proprietary to the sponsor. Any outcome results are strictly confidential and must not be divulged to anyone who is not a member of the DSMC, except as specified in the policy.

DSMC Membership

The Chair of the DSMP is responsible for overseeing all aspects of data monitoring, ensuring the safety of participants in all clinical trials, particularly institutionally-sponsored, investigator-initiated trials, and verifying the validity and integrity of the data provided to the DSMC.

Cindy Varga, MD; Hematology and Oncology (DSMC Chair)
Gustavo Mercier, MD Radiology
Peter Everett, MD, Hematology and Oncology
Omar Eton, MD, Hematology and Oncology
Radhika Sane, Pharm D, Investigational Pharmacy
Bhavesh Shah, Pharm D, Investigational Pharmacy
Annie Jose, Cancer Clinical Trials Program
Mary-Tara Roth, Clinical Research Resources Office

Theodore Colton, ScD. Director of Cancer Biostatistics Resource (*ad hoc*)
Jack Clark, PhD (Health Policy and Management) (*ad hoc*)

The members of the multi-disciplinary DSMC include representatives from hematology and medical oncology, investigational pharmacy, health policy, the Boston University Clinical Research Resources Office, and the Cancer Clinical Trials Office.

Meeting Schedule
DSMC meetings will be held at least every three months. Special meetings (in person, via telephone or electronic) may be convened when necessary, for urgent concerns regarding patient safety or data integrity. The PI or the Scientific Review Committee may request unplanned monitoring of a given study. Data will be collected and analyzed approximately four weeks before the DSMC meeting. A copy of all the analyses will be mailed to the DSMC members before the meeting. The timing for ending material will allow two (2) weekends for the DSMC members to review it.

Data and safety monitoring and study reviews take place until all subjects have completed any protocol-related activities and are beyond the time during which study-related adverse events may occur.

DSMC Procedures

The DSMC may vote to take one of the following actions for each protocol reviewed:

Full Approval: enrollment may continue; no outstanding questions regarding toxicity or accrual.

Conditional Approval: enrollment may continue conditional upon satisfactory response by the principal investigator to the DSMC concerns regarding toxicities and/or accrual and/or new information relevant to the trial.

Suspension: enrollment immediately suspended pending principal investigator response to the DSMC concerns regarding toxicity and/or accrual patterns.

Closure: study closed due to unacceptable toxicity and/or accrual patterns.

The presence of three or more of the DSMC voting members constitutes a quorum.

All DSMC decisions are conveyed in writing to the study principal investigator and the Scientific Review Committee.

The CCTP Protocol Review and Monitoring System (PRMS) Administrator serves as recording secretary to the DSMC and is responsible for coordinating all meetings and communications.

Study principal investigators may appeal DSMC decisions in writing to the chairman of the DSMC.

Temporary or permanent suspension of any BMC investigator-initiated clinical trial by the DSMC will be reported immediately to the BUMC IRB and any relevant study collaborators (e.g. pharmaceutical companies). The monitoring plan is amended as to reflect any new monitoring requirements.

If the suspension is temporary, the BUMC IRB and any relevant study collaborators will also be notified in a timely manner regarding the resolution of the issues that caused the suspension, and the date that the suspension was lifted.

This committee was established in January, 2010 and its procedures will be continually reviewed and refined until a more permanent charter can be adopted.

BUMC Cancer Center Protocol Review and Monitoring System (PRMS)

Please submit this form two weeks prior to the scheduled DSMC Meeting and attach the following documents:

- Electronic copy of the protocol
- Spreadsheet including: date of enrollment, pt initials, pt number, gender, age, race, status on study
- A copy of the Data Safety Monitoring Plan outlined in the INSPIR application.
- SAE reports, follow-up reports, and outcome reports

BUMC PROTOCOL #: **Activation DATE:**

STUDY STATUS: Open to Accrual **DATE OF LAST REPORT:**

PROTOCOL TITLE			
7. Principal Investigator; Primary Research Nurse/Associate			
8. PROTOCOL ACTIVITY			
Planned Accrual Duration:			
Date First Patient Enrolled at BMC:		Local Accrual to Date / Goal: National Accrual to Date / Goal:	/ /
# Consented Since Last Report:		Accrual Since Last Report:	
# Eligible Since Last Report:		# Ineligible Since Last Report:	
9. Study Status: (include # of Patients currently active, in follow-up, completed or expired.)			
10.			
11.			
12. PROTOCOL-SPECIFIC INTERIM ANALYSIS (if applicable)			
13.			
14.			
15.			
16. SAE/UPSER REPORTING SINCE LAST REPORT: List event, causality attribution, expected/not expected, patient study ID number, date of occurrence (include cycle #, Day #), and date IRB notified. Attach SAE reports, follow-up reports, and outcome reports.			
1]			
2]			
3]			
PATIENTS COMPLETED/OFF PROTOCOL SINCE LAST REPORT w Provide reason [progression, death (include cause), toxicity (specify), completed therapy, etc]. Provide detailed supplemental information for patients off study treatment due to toxicity or death.			
PROTOCOL DEVIATIONS/EXCEPTIONS SINCE LAST REPORT w Include both *purposeful and accidental* variances in the approved procedures outlined for a study in its IRB approved protocol; provide date reported to Regulatory or IRB. Attach any protocol deviation forms.			
OTHER COMMENTS			
Investigator Signature & Date:		**Data Manager Signature & Date:**	

Figure 1 shows the procedures involved in data and safety monitoring.