IDELALISIB POST ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) IN B CELL DERIVED MALIGNANCIES: A PHASE 1 DOUBLE BLINDED RANDOMIZED PLACEBO TOXICITY TRIAL

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1. INTRODUCTION

For all relapsed B cell derived hematologic malignancies, allogeneic bone marrow transplantation (allo BMT) is often the most definitive curative intent therapy. Historically, there have been four obstacles decreasing overall survival (OS) associated with allo BMT: preparative conditioning toxicity, donor availability, graft-versus-host-disease (GVHD) and disease relapse. Reduced intensity conditioning (RIC) regimens have dramatically reduced alloBMT toxicity and have expanded the use of this therapy to patients up to 75 years of age.(1-3) The use of alternative donors has resulted in an average of 2.7 donors for each patient in Johns Hopkins University.(4) The use of post-transplant cyclophosphamide has reduced the incidence of Grade III-IV GVHD to 6% - 11%.(5-7) However, disease relapse after successful engraftment during allo BMT remains the limiting factor for improving overall survival. (5, 6, 8)

Currently, in order to improve OS, the BMT program at JHH has recently focused on the introduction of anti-neoplastic therapy post transplantation. We use the allo HSCT as a platform to allow a new intolerant immune system to interact with a post allo HSCT biologic or therapeutic intervention. Currently, to improve overall survival, the focus of the BMT program at JHH the introduction of anti-neoplastic therapy post transplantation: where the allo BMT serves as a platform to allowing a new intolerant immune system to interact with the post allo BMT intervention. The importance of post BMT therapy has been made evident with tyrosine kinase inhibition (TKI) in Ph+ ALL and Ph+ CML, where patients who had disease progression while on TKI therapy pre-allo BMT enjoy marked improvement in OS when TKI is part of a maintenance program (9-12); the use of DNA hypomethylation agents after allo BMT for relapsed myeloid malignances (13); or the use of rituximab after allo BMT in follicular lymphoma (PMID 26183076). At JHH we are currently, utilizing post allo BMT: TKI in Ph+ leukemia's, sorafenib and other multi-kinase inhibitors in FLT3-ITD AML, and 5-azacytidine in MDS patients.

Previous experience with Idelalisib, an orally-administered, selective inhibitor of Phosphoinositide 3 kinase (PI3K)-δ is extremely effective in inducing partial responses to complete responses in many B-cell derived malignancies. Considering this published track record, idelalisib should be studied in the post allo BMT setting. While evaluating patients using a pre-transplant conditioning approach in patients with high risk CLL based on cytogenetics, would also be of interest, recent NCCN recommendations list idelalisib as the treatment option in this cohort, hence our focus on post-transplant maintenance. Moreover, a non-disease specific but treatment oriented selection of patients will likely reveal a clinically significant endpoint signal more quickly. However, before embarking on a large randomized trial to determine the impact Idelalisib has on the relapse-free survival after allo BMT for B cell derived hematologic malignances, a phase 1 toxicity/safety trial is warranted.

Here at JHH we have one of the world's largest experiences with alloHSCT. We propose a double blinded randomized phase I placebo trial where all patients who have undergone alloHSCT for a B-cell derived hematologic malignancy be offered either idelalisib 100mg or placebo twice daily for 180 days starting approximately 90 days after their HSCT.

While Idelalisib is a selective PI3K inhibitor, most affecting the p110□□isoform, the expression of PI3K on regulatory NK cells requires careful clinical study. (14) In fact, PI (3) K□□blockade can affect suppressor T_{reg} function which could alter the incidence of GVHD in this population. (15) In addition, literature data has shown

targets upstream of PI3K, i.e. Syk, also show evidence of B cell modulation in the transplant setting (Allen et al., 2014)

1.1. HYPOTHESIS

Idelalisib can be safely used as maintenance therapy after allo HSCT in patients with B cell derived hematologic malignances.

2. OBJECTIVES

2.1. PRIMARY ENDPOINT

To evaluate the safety of idelalisib, as post alloHSCT maintenance therapy in patients with B-cell hematologic malignancies, by comparing to placebo.

2.2. SECONDARY ENDPOINT

Event free survival at one year

2.3. TERTIARY ENDPOINTS

To explore the association between potential biomarkers, clinical activity and/or toxicity of Idelalisib administered after allogeneic BMT. Multi-color flow cytometric analyses of immune markers pre- and post-treatment, high-throughput DNA sequencing of rearranged TCRβ CDR3 regions from T cell genomic DNA, cytokine measurements, and immunohistochemistry is planned. In addition, we may perform exploratory gene expression analysis of immune biomarkers in the bone marrow aspirates and whole or targeted exome sequencing of the lymphoma cells.

3. INCLUSION/EXCLUSION CRITERIA

3.1. INCLUSION CRITERIA

1. ≥18 years of age
2. Patients having undergone alloHSCT to treat a B-cell derived hematologic malignancy: accepted alloHSCT regimens include: myeloablative or reduced intensity conditioning from any donor (matched, partially mismatched or cord) and any source (peripheral blood, bone marrow, or cord).
3. T bili ≤ 1.5 mg/dL except for patients with Gilbert's syndrome or hemolysis
4. AST, ALT and alk phos all < 2.5X ULN
5. Karnofsky performance score ≥ 40
6. ECOG ≤3
7. For women of childbearing potential, a negative serum or urine pregnancy test with sensitivity less than 50 mIU/m within 72 hours before the start of study medication.
8. Use of two forms of contraception with less than a 5% failure rate or abstinence by all transplanted patients for a minimum of 1 month after the last dose of Idelalisib. For the first 60 days post-transplant,

transplant recipients should be encouraged to use non-hormonal contraceptives due to the potential adverse effect of hormones on bone marrow engraftment.

9. Ability to receive oral medication.
10. Ability to understand and provide informed consent.

3.2. EXCLUSION CRITERIA

1. ECOG >3 (Karnofsky <40%)
2. ALT, AST >2.5 ULN or total bilirubin >1.5 ULN (not attributable to Gilbert's)
3. Women who are pregnant or breastfeeding.
4. Exclude if patient has cirrhosis or is currently being actively treated for hepatitis C.
5. History of positive HIV-1 or HIV-2 serologies or nucleic acid test.
6. Active hepatitis B infection as documented by positive Hepatitis B PCR assay
7. Use of investigational drug, other than the study medications specified by the protocol, within 30 days of transplantation.
8. Receipt of a live vaccine within 30 days of receipt of study therapy.
9. > Grade II aGVHD
10. The presence of any medical condition that the Investigator deems incompatible with participation in the trial
11. Subjects who are required to use a medication classified as a strong CYP3A inducer of inhibitor. An exception can be made for those patients required to take azole based antifungal prophylaxis and/or treatment.

3.3. ENROLLMENT

Approximately 60 patients who have undergone allo BMT for B-cell derived hematologic malignancies.

4. STUDY PROCEDURES

- Idelalisib, 100mg twice daily, starting day +90 (+-/ 10 days) and at least five days after the discontinuation of filgrastim, if ANC greater than 1000 and PLT 50>Gi/L and continued through day +270. Patients will have a CBC with platelet count and comprehensive metabolic panels performed every 14 days beginning at day +90 through day +120, then monthly through day +270.

Patients will be monitored for treatment-limiting toxicities defined as Idelalisib interruption for >14 days, or any other Grade 3 or higher adverse events as defined by CTCAE IV not captured in the protocol for dose de-escalation. All Adverse events will be collected and assessed for causality but only AEs Grade 2 and higher will be recorded on the Master AE log. Patient's idelalisib will be dose adjusted for the expected toxicities of idelalisib including pneumonitis, hepatitis, neutropenia, thrombocytopenia and loose stools.

4.1. PREMATURE DISCONTINUATION OF STUDY THERAPY

Study therapy is defined as initiation of any study-mandated therapies and study procedures described in section 4.0.

Study therapy will be discontinued for the following reasons:

- Adverse experience. If a participant suffers from an adverse experience that, in the judgment of the Principal Investigator, may present an unacceptable consequence or risk to the participant.
- Intercurrent illness or infection. If during the course of the study a participant develops an illness or infection that is not associated with the condition under study and that requires treatment not consistent with protocol requirements; or, if a participant develops an intercurrent illness that in the judgment of the Principal Investigator justifies discontinuation.
- Protocol violation. If a participant cannot comply with the study protocol and the protocol deviations are sufficient to jeopardize his or her well-being or the integrity of the study.
- Pregnancy.
- Investigator discretion. If the Investigator determines that the study therapy is no longer in the best interests of the participant.
- If the participant is unwilling or unable to continue on study therapy.

4.2. PREMATURE TERMINATION OF A PARTICIPANT FROM THE STUDY

Participants will be prematurely terminated from the study for the following reasons:

- **Withdrawal of consent.** If for any reason a participant withdraws consent during the study they will be terminated from the study. All information and biospecimens collected from the participant prior to their withdrawal of consent will continue to be utilized by the study.
- **Failure to return.** Participants who do not return for visits and who do not respond to repeated attempts by the site staff to have them return will be considered *lost to follow-up*.

4.3. TABLE 1. SCHEDULE OF ASSESSMENTS

	Screening and Baseline (	Cycle 1, Day 1 Day +90 (± 10 Days)	) Cycle 1, Day 15	(± 7 Days) Cycles 2-6, Day 1	30 days Post last dose	Month 12 (± 14 Days)
Informed Consent[a]	Days 60 -100					
Medical History	X					
Physical Exam	X	X		X	X	X
AE Assessment	X	X		X	X	X
CBC with diff	X	X	X	X	X	X
Comprehensive metabolic panel e (CMP) [b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
PT, PTT, INR	X					
Serum □-HCG (if applicable)	X					
CMV PCR[d]	X[d]	X	X	X		
Dispense Idelalisib		X		X		
Standard of care per institution						
T-cell chimerism	X					X
Bone marrow biopsy (as std of care)	X					X
aGVHD/cGVHD assessments	X	X	X	X		X
Correlative studies[c,]	X	X		X[c]		X

[a]Informed consent will be collected beginning on Day +60 after BMT until Day +100.

[b] CMP to include BUN, creatinine, sodium, potassium, chloride, AST, ALT, total bilirubin, alkaline phosphatase.

[c] Additionally specimens should be obtained from peripheral blood and bone marrow collections as a part of routine clinical care such as GVHD, toxicity and/or disease relapse Correlative peripheral blood samples should be collected on Day 1 of every other cycle beginning with Cycle 2

[d]Cytomegalovirus (CMV) viral load assay will be monitored by PCR every 14 days between days +90-and day +120, then monthly through day +270: treat according to BMT policy guidelines.

5. KNOWN TOXICITIES AND DOSE ADJUSTMENTS

5.1. KNOWN TOXICITIES OF IDELALISIB

Idelalisib is FDA approved for the treatment of relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular B-cell non-Hodgkin lymphoma. Idelalisib may cause:

- ALT/AST elevations and hyperbilirubinemia (most frequently occurs within the first 12 weeks of treatment); incidence of serious hepatotoxicity: 14.0%
- Diarrhea (mean time to occurrence 7.2 months); incidence of serious/severe diarrhea: 14.0%
- Pneumonitis; incidence <5%
- Neutropenia: Grade 3 or 4 neutropenia occurs in approximately 31% of patients receiving the 150mg bid dose.
- Rash: Grade 3 or 4 rash occurred in approximately 21% of patients receiving the 150mg BID dose.
    - CYP3A affects: CYP3A inducers can reduce the AUC of idelalisib by 75%; CYP3A inhibitors can increase the AUC of idelalisib by 1.8 fold; idelalisib is strong CYP3A inhibitor. A list of these drugs can be found in appendix 4. Importantly, with direct relevance to this study is the lack of data supporting strong interaction with voriconazole. Azoles are often the medication of choice for patients with suspect fungal or anti-bacterial non-responsive fevers during alloBMT. The elimination of idelalisib is predominantly mediated by the hepatic pathway. Idelalisib is primarily metabolized by aldehyde oxidase with a lesser involvement of cytochrome P450. The major metabolite of idelalisib is GS-563117. Data indicate that CYP3A inhibition by concurrent use of azoles may result in modestly higher exposures of idelalisib, but the change is not of clinical relevance[21]. In this study, as the dosing of idelalisib is already reduced to 100mg bid to provide additional risk mitigation. Additionally, patient's receiving azole therapy while on idelalisib will have serum levels monitored to adjust to target levels.

Therefore, to protect patients in this study the following measures are employed:

- Patients will have comprehensive metabolic panels performed every 2 weeks through day +120, then monthly through day +270.
- Patients post alloBMT may develop intestinal aGVHD which may present with diarrhea or ileus. All patients with $\geq$3 grade diarrhea will also be evaluated for aGVHD in addition to idelalisib dose modification.
- Patients post alloBMT may develop aGVHD which often presents with a generalized cutaneous rash. All patients with $\geq$3 grade rash will also be evaluated for aGVHD in addition to potential idelalisib dose modification.
- Patients post alloBMT often develop late neutropenia after achieving neutrophil recovery. To help limit the depth of neutropenia that could be attributable idelalisib, idelalisib will be dosed at 100mg bid, the suggested dose reduction for patients experiencing an ANC <.5Gi/L while on the standard 150mg bid dosing schedule
- CYP3A interactions. Commonly, patients post alloBMT require azole based antifungal prophylaxis and/or treatment. Patients receiving posaconazole or voriconazole will have these levels checked every 14 days while receiving idelalisib.
- Additionally, in the post alloBMT patient population, novel toxicities need to be considered, therefore, stopping rules will be established to stop this study, if compared to the placebo control the incidence of GVHD or any other toxicity caused by idelalisib or placebo causes discontinuation at a rate differential of >10%.

5.2. DOSE ADJUSTMENT OF IDELALISIB OR PLACEBO

Study drug consists of oral idelalisib or placebo tablets. The standard dose of idelalisib for this protocol is 100mg idelalisib tablets (orange, oval shaped and film coated) or matched 100mg silicified microcrystalline cellulose placebo tablets taken twice a day.

When necessary, idelalisib or matched placebo dose can be adjusted to 100 mg taken once a day. Based on current PK data supplied by Gilead, a clinical trial examining various idelalisib doses in combination with a second drug held at a fixed dose found that the steady state AUC for idelalisib 100 mg QD dosing reduced patient idelalisib exposure by ~30% as compared to 50 mg BID dosing. The investigators further determined that the second drug did not influence the idelalisib drug concentrations at the studied doses. Additionally, Gilead study 101-02 demonstrated AUC0–24h were similar, 19,600 and 16,300 ng.h/mL for 150mg BID and 300mg QD, respectively.[21] Due to this data, we are confident that a dose reduction from 100mg BID to 100mg tablets taken once daily will sufficiently reduce patient exposure to idelalisib in the context of this study.

PNEUMONITIS

Non-infectious pneumonitis can occur with Idelalisib use and occurs in allogeneic bone marrow transplant recipients. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

If idiopathic, symptomatic pneumonitis occurs, stop study drug until symptoms resolve to less than or equal to grade 1. The use of corticosteroids may be indicated. Study drug may be reintroduced at a dose of 100 mg once daily. If idiopathic pneumonitis recurs at the reduced dosing level, then discontinue study drug permanently.

HEPATOTOXICITY

Transaminitis and hyperbilirubinemia can occur with idelalisib use and are also common in allogeneic bone marrow transplant recipients. For patients experiencing an AST/ALT or bilirubin >5x ULN that is unexplained by other factors, hold study drug until the parameter is $\leq$ 2ULN and restart at 100mg once daily. If the parameter should rise again >5 ULN, discontinue study drug. For AST/ALT >20x ULN (or Bilirubin >10x ULN), regardless of attribution, study drug should be permanently stopped.

DIARRHEA

Diarrhea can occur with idelalisib use and is also common in allogeneic bone marrow transplant recipients. Prior to major pharmacologic intervention, common infectious causes of loose stooling should be evaluated. For loose stools, in the absence of major infections, anti-motility agents may be offered and/or light steroid preparations. For patients with significant stooling, >1L daily, hold study drug and consider colonic biopsy if there is evidence to suggest aGVHD. Once stooling is <0.5L day, restart at 100mg oncedaily. If stooling should

again increase to >1L daily, discontinue study drug. For life-threatening diarrhea, study drug should be permanently stopped.

NEUTROPENIA AND THROMBOCYTOPENIA

Neutropenia and thrombocytopenia can occur with idelalisib use and are also common in allogeneic bone marrow transplant recipients. For ANC < 500 or PLT < 25,000, monitor CBC with differential weekly, hold study drug until ANC >1,000 and PLT count >50,000 and restart at the original dose. If a subject develops ANC < 500 or PLT < 25,000 a second time, hold study drug until ANC >1,000 and PLT count >50,000 and restart at 100mg once daily. If a subject who is on 100mg once daily develops ANC < 500 or PLT < 25,000, discontinue study drug.

Acute GVHD: Patients with symptomatic aGVHD will be treated as per institutional guidelines. If after seven days of therapy there is evidence of progressive aGVHD, study drug will be stopped for at least seven days. If it is determined that study drug was not causative of the aGVHD it may be restarted at the discretion of the primary oncologist. If after 14 days of active therapy there is no improvement of the aGVHD, study drug will be stopped for at least seven days. If it is determined that study drug was not causative of the aGVHD persistence it may be restarted at the discretion of the primary oncologist.

LATE ONSET NEUTROPENIA (LON)

Rituximab- associated LON is defined by most investigators as grade III-IV neutropenia (ANC <500 cells/µL), occurring after the ANC has recovered to within normal limits, but within 3-4 weeks after the last dose of rituximab[22] . If subject develops LON after rituximab use or which per medical judgement can be attributed to another cause outside of the use of idelalisib, the subject may receive the appropriate medical or surgical intervention without being taken off study or having study drug held. If, in the judgment of the attending physician, the subject has had no resolution of symptoms after receiving standard intervention, study drug will be held until ANC >1000.

6. STUDY STATISTICS

This is a phase I study of Idelalisib, an orally-administered, selective inhibitor of Phosphoinositide 3 kinase (PI3K)-δ. It has been successfully used pre-transplant to induce partial and complete responses in many B-cell derived malignancies. In this study Idelalisib will be evaluated in the post-transplant setting. Patients receiving a standard of care allogeneic hematopoietic stem cell transplant from any source: cord, marrow, or peripheral blood will be eligible. Patients will be randomized in a 2:1 ratio to either 100 mg Idelalisib twice daily from day 90 (±10 days) following transplant, Arm A, or a placebo, Arm B, and monitored for toxicity until day 270.

Study treatment plan: Idelalisib day +90 [+/- 10 days), 100mg twice daily, and at least 5 days after the discontinuation of filgrastim if ANC is greater than 1,000 and PLT 50>Gi/L and <grade 2 aGVHD. Patient's Idelalisib will be dose adjusted for the expected toxicities of Idelalisib including pneumonitis, hepatitis, neutropenia, thrombocytopenia and loose stools.

Primary endpoint and design: The primary goal of this study is to evaluate the safety of Idelalisib as post-transplantation maintenance in patients undergoing an allogeneic BMT. In addition to the allowed dose reductions, a safety monitoring plan will be implemented to ensure that other treatment-limiting events are not elevated. The study will be monitored between the date of randomization and day 270 post-transplant. For safety monitoring, treatment-limiting toxicities will be defined as Idelalisib interruption for >14 days, or other grade 3 or higher adverse events as defined by CTCAE IV not captured in the protocol for dose de-escalation. The trial will assume that, *a priori*, the probability of these events in both arms of the study will follow a Beta (0.10, 0.90) prior distribution. This distribution corresponds to an assumption that 10% of patients might experience a treatment-limiting toxicity.

Sample size/accrual Rate: The accrual rate for this study is expected to be 20 patients per year. The total sample size will be 45 patients, 30 on the Idelalisib arm (Arm A) and 15 on the control arm (Arm B). The safety objective of this trial is based on the precision of estimating the specified treatment-limiting toxicity events. An approximation to the precision will be made using binomial confidence intervals. Thirty patients on the Idelalisib arm will allow us to estimate the proportion of patients experiencing post-transplant events with a precision of ± 0.19%.

Interim analyses and operating characteristics: For monitoring we will compute the posterior probability of a treatment-limiting toxicity between day 90 and 270 in each arm of the study, given the data and prior distribution, Beta(0.10, 0.90), and evaluate whether to hold accrual after fixed cohorts of patients. Monitoring will occur in groups of 15 patients, beginning after the first 10 enrolled on Arm A. The maximum sample size will be 45 patients, 30 in Arm A and 15 in Arm B. The stopping rule will recommend a safety review if it becomes clear that the posterior probability of a treatment-limiting toxicity in Arm A exceeding Arm B by 0.10 is 75% or greater. Operating characteristics of the study with Arm B treatment-limiting toxicity of either 5%, Table 1, or 10%, Table 2, and varying toxicities in Arm A are based on 1,000 simulations of the trial.

Table 1. Scenarios with control arm (Arm B) treatment-limiting toxicity of 5%
Both arms prior: Beta (0.10, 0.90), assumes prior for toxicity is 10%, delta of 0.10, and 75% cutoff.
2:1 randomization Total N=45

	Delta=0.10	Delta=0.10
Scenario: Control, Idelalisib	**Stopped for toxicity**	**Avg. sample size Control, Idelalisib**
1: 0.05, 0.05	**1.3%**	**14.9, 29.8**
2: 0.05, 0.10	**6.8%**	**14.4, 28.8**
3: 0.05, 0.15	**19.2%**	**13.4, 26.8**
4: 0.05, 0.20	**32.4%**	**12.3, 24.7**
5: 0.05, 0.25	**53.1%**	**10.5, 21.0**
6: 0.05, 0.30	**68.2%**	**9.3, 18.7**
7: 0.05, 0.35	**82.3%**	**8.0, 16.0**
8: 0.05, 0.40	**89.8%**	**7.1, 14.2**
9: 0.05, 0.45	**94.9%**	**6.3, 12.6**

Table 2.
Scenarios with control arm (Arm B) treatment-limiting toxicity of 10%
Both arms prior: Beta(0.10, 0.90), assumes prior for toxicity is 10%, delta of 0.10 and 75% cutoff.
2:1 randomization Total N=45

	Delta=0.10	Delta=0.10
Scenario: Control, Idelalisib	**Stopped for toxicity**	**Avg. sample size Control, Idelalisib**
1: 0.10, 0.10	**4.9%**	**14.6, 29.1**
2: 0.10, 0.15	**12.0%**	**13.9, 27.8**
3: 0.10, 0.20	**27.9%**	**12.7, 25.4**
4: 0.10, 0.25	**44.3%**	**11.4, 22.8**
5: 0.10, 0.30	**59.0%**	**10.1, 20.2**
6: 0.10, 0.35	**70.7%**	**9.3, 18.5**
7: 0.10, 0.40	**83.4%**	**8.1, 16.1**
8: 0.10, 0.45	**90.0%**	**7.3, 14.5**
9: 0.10, 0.50	**94.4%**	**6.6, 13.1**

Secondary endpoint:

1. Event-free survival at one year.

Analysis Plans:
Toxicities will be summarized descriptively by grade and type. Cumulative incidences of aGVHD, relapse, and NRM will also be computed using Fine and Gray's method for competing risks. Treatment of relapse/progression, graft failure, and death are considered competing risks for GVHD; relapse/progression is a competing risk for NRM; and death before relapse/progression is a competing risk for relapse/progression. In addition, we plan to report aGVHD incidences with only graft failure and death regarded as competing risks.

Using the Kaplan-Meier method, the probability of 1-year event-free survival will be estimated and reported with 95% confidence intervals. The proportions of patients who are event-free at 1 year will also be estimated with a 95% exact binomial confidence interval.

7. CORRELATIVE STUDIES

7.1 RATIONALE AND OUTLINE OF CORRELATIVE STUDIES

The overarching goals of our correlative studies are to:

i) Characterize the effect of Idelalisib on allogeneic T and B cells, particularly on their re-distribution, in vivo expansion, activation, and effector differentiation after treatment
ii) Identify potential predictive biomarker candidates to allow for better selection of patients after alloBMT who may benefit or whom are likely to have toxicity from Idelalisib therapy.
iii) Characterize the mechanisms of relapse after Idelalisib such as B cell and T cell dysfunction.

Hypothesis: We hypothesize that Idelalisib administration will have an effect on GVHD modulation. This prediction is based on the data suggesting that PI3K pathway is activated in activated/memory T cells responsible for autoimmunity (16). Interestingly, Ali et al., have recently shown that PI3K inactivation results in the disruption of two tumor-associated immune-suppressive cell types- regulatory T cells and myeloid-derived suppressor cells (17). Thus, we also hypothesize that p110 inhibition with Idelalisib can enhance allogeneic antitumor immunity post-transplant that can be measured as increased TCR diversity and the emergence of unique TCR clonotypes.

Flow Cytometry Studies: We will perform multi-color flow cytometry on peripheral blood (PB) and bone marrow (BM) specimens before and after Idelalisib treatment using three pre-determined panels of mAbs including but not limited to those specific for CD3, CD4, CD8, PD-1, CD45RA, CCR7, CD25, CD27, CD28, CD69, Ki-67, T-bet, CD127, FoxP3, HLA-DR, CTLA-4, TNFRII, TIM3, LAG-3, CD160, 2B4, BTLA, KLRG-1, CD16, and CD56. This multi-color approach allows examination of different CD4+ and CD8+ T cell subpopulations (expressing CD45RA, CCR7, CD27, and CD28), phenotypic separation of human CD4+FoxP3+ T cells into three distinct subpopulations as well as assessment of their proliferative status (% Ki-67 positive cells). (18) The expression of CD69, HLA-DR and TNFRII will be measured to characterize T cells activation status and the expression of co-inhibitory molecules (PD-1, TIM3, LAG-3, CD160, 2B4, BTLA, KLRG-1) will be studied. Natural killer cells (NK), NK-T cells will be enumerated using CD16 and CD56 (NK/NK-T cells). Additionally effects of Idelalisib on myeloid-derived suppressor cells and B cell depletion post-transplant will be assessed. As a part of PBMCs collection and mononuclear cell isolation we will also collect plasma that will be stored and used for measurement of defined cytokines (IL-2, IL-6, IL-10, IFN-γ,TNF-α) to assess Idelalisib -induced global T cell activation or for proteomic analysis of defined molecules associated with GVHD (proteomic studies on PTCy-based platforms are being prepared for publication (20)).

Molecular studies: Immune Profiling of T cell Repertoire: The studies proposed will evaluate the T cell receptor (TCR) diversity in T cells isolated from PB and BM from patients before and after treatment with Idelalisib on the parent clinical trial. We will determine TCR diversity and clonal composition using a molecular

and computational approach based on high-throughput DNA sequencing of rearranged TCRβ CDR3 regions from T cell genomic DNA. This approach allows direct measurement of the TCRβ CDR3 region sequence diversity in any arbitrarily complex population of T cells, and also permits quantitative description of the clonal composition of the population. (19) The Luznik laboratory in collaboration with the E. Warren laboratory from Fred Hutchinson Cancer Research Center (FHCRC) have performed extensive monitoring and tracking of the TCR repertoires in patients undergoing alloHSCT (manuscript in preparation). We are utilizing an established multiplex PCR strategy to amplify the CDR3 region of the TCR, spanning the variable region formed by the junction of the V, D and J segments and their associated non-template insertions followed by Illumina-based sequencing methodology, an well-characterized methodology developed by Adaptive Technology (http://www.adaptivebiotech.com/technology/). Sequencing is followed by comprehensive bioinformatics analyses focused on determining the diversity of the T cell and B cell repertoires as well as the entropy and clonality of each repertoire consistent with previous studies. Through these ongoing studies we have developed substantial experience not only in using and analyzing DNA retrieved from unsorted PBMCs but also from sorted T cells subpopulations (naïve vs memory vs regulatory), paired PB and BM samples and as well from DNA retrieved from FFPE archived tissues.

The long-term goal of this correlative work is to uncover biomarkers that in future may predict better integration of Idelalisib post-transplant. This correlative work will also provide deeper insight into the, effects of Idelalisib on GVHD and allogeneic anti-tumor immunity as well as on the mechanisms of failure to eradicate B cell malignancies after Idelalisib treatment.

7.2 Analysis of Correlative Endpoints

The analyses of pre- and post-treatment PB and BM specimens for immune parameters will be descriptive and graphical in nature. Data will be summarized for each cohort separately. The change in flow values at each time point after Idealisib relative to the baseline value will be will checked for skewness and log-transformed as appropriate. The changes will be modeled using mixed-effects, linear regression models that included fixed effects for time and a random effect for the patient to account for within-patient correlation of measurements. To explore potential differences in the change in flow values across patient subgroups, interaction terms will be included in the regression models. Post-treatment changes in gene expression in immune gene signaling circuits in tumor biopsies and PB will be summarized with descriptive statistics and correlated with clinical outcomes.

7.3 OPERATING PROCEDURES FOR SPECIMEN COLLECTION

Peripheral blood and bone marrow specimen collection will be performed as delineated in the Table 1 Schedule of Assessment Section 4.3 and additionally at the times when peripheral blood and bone marrow collections are performed for clinical care such as GVHD, toxicity and/or disease relapse.

Bone marrow: 4 x 8mL will be collected in green top sodium heparin tubes (~20-30 mL). Re-adjustment of the direction of bone marrow aspirate needle should take a place after each 10 cc is collected to prevent hemodilution. At the time of collection, green top tubes must be thoroughly mixed to prevent clotting.

Peripheral blood: 5x8mL green top sodium heparin tubes of blood (~40mLs) will be collected at each time point.

Specimens should be labeled with the patient's study number (given at the time of registration), study number, sample collection date and time, and sample source (PB or BM). Sample collection date and time, and sample source (PB or BM) will be recorded on correlative collection worksheet and copy included with delivery. All data should be kept in laboratory log. At each sampling time, BM and PB mononuclear cells (PBMC) will be processed via Ficoll density gradient centrifugation. The washed cells will be counted, triaged for DNA isolation, and viably cryopreserved using a controlled-rate freezer with transfer to the vapor phase of liquid nitrogen for long-term storage (Luznik laboratory).

The Sidney Kimmel Comprehensive Cancer Center (SKCCC) specimens should be delivered to the Luznik laboratory immediately after collection.

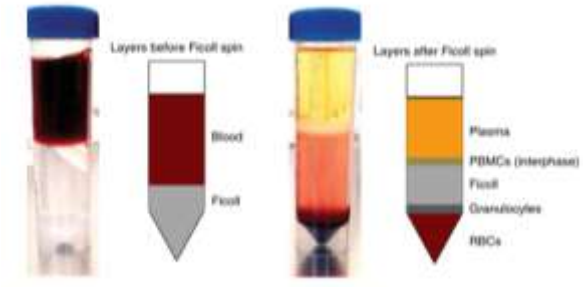
Specimen collection / processing: PB and BM specimens should be collected as outlined in the Trial Flow Chart 6.0.

7.3 FREEZING PROTOCOL (SOP)

1. Prepare 50mL falcon tubes with Ficoll density grade media (Histopaque)
    - Ratio Ficoll : blood should be 1:1
    - Do not exceed 20mL Ficoll to 20mL blood (i.e. total volume of 40mL)

2. Slowly layer blood on top of Ficoll
    - Use whole blood or marrow aspirate, do not dilute with PBS or anything else
    - Be careful not to mix the two layers

3. Centrifuge: spin at the following settings:
    - 1240rpm (=364G)
    - 20 Celsius
    - Break off
    - 30min



4. Prepare 6 small Eppendorf tubes
    - Take off 6 x 500ul of plasma (top layer; blood only; not for BM aspirate) and put it into Eppendorf tubes
    - Be careful not to get into any layer but the plasma layer
    - Long term storage in -80 Celsius freezer

5. Soak up PBMC layer with transferring pipette and put it into a new 50mL Falcon tube
    - Fill up with PBS up to 45mL, vortex
    - Centrifuge: Spin at 1240 rpm (=364G), 4 Celsius, break high, for 5 minutes

6. First wash

- Dump supernatant
- In case of visible RBC contamination add 1Ml of lysing buffer to the cell pellet, vortex, and leave for 1 minute. Then add 20mL of PBS
- If there is no RBC contamination only add 20mL of PBS and vortex
- Centrifuge: Spin at 1240 rpm (=364G), 4 Celsius, break high, for 5 minutes

7. Second wash
    - Dump supernatant
    - just add 20mL of PBS and vortex
    - Centrifuge: Spin at 1240 rpm (=364G), 4 Celsius, break high, for 5 minutes

8. Count cells
    - Dump supernatant
    - add 1mL of PBS and vortex thoroughly
    - take 10ul out and mix with 90ul of trypan blue
    - count in hematocytometer

Study # _____
Pt ID# _____
Timepoint: _____
Cell count: _____
Date(time): _____

Blood or Marrow

9. Prepare freezing tubes and media
    - Put cells in the meantime on ice
    - Freezing media: FBS containing 10% DMSO
    - 1.8mL vials labeled with study #, time point, cell count, date, type of specimen,

10. Final spin
    - Add 20ml of PBS to the cells, vortex
    - Centrifuge: Spin at 1240 rpm (=364G), 4°C, break high, for 5 minutes

11. Freeze cells - General rules
    - PBMCs: 1.5mL freezing media per 10 million cells (=1 vial)
    - BMMCs: 1.5mL freezing media per 30 million cells (=1 vial)

12. Freezing
    - Put vials into Mr. Frosty® (container with Ethanol, that gradually cools down samples) and put into -80 Celsius fridge for about 24 hours
    - After 24 hrs (up to 48hrs) transfer vials into liquid nitrogen tanks (to minimize temperature fluctuations make sure you transport them there on dry ice)

Considerations regarding freezing and shipping

- Samples should optimally be processed the same day
- If there is a sample coming in late, keep it in the fridge (in 4◦C) overnight and process them early the next morning.

- Samples processed should be stored in -80 Celsius for 24-48 hours and get transferred into liquid nitrogen thereafter
- If there are no liquid nitrogen tanks available, it's permissible to keep samples in -80 Celsius for up to 2 weeks, but no longer.

Important considerations:

1. All work should be done using standard BSL2 procedures (blood and body fluid precautions).
2. Maintain a clean workspace and use a containment laminar airflow hood when possible.
3. Minimize the chance of contamination.
4. Work quickly but methodically.
5. Keep tubes closed as much as possible and work quickly.
6. Change gloves frequently and maintain situational awareness

8. RISKS

8.1. IDELALISIB RISKS

Known toxicities of idelalisib: idelalisib is FDA approved for the treatment of relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular B-cell non-Hodgkin lymphoma.

Idelalisib may cause:

1. ALT/AST elevations and hyperbilirubinemia (most frequently occurs within the first 12 weeks of treatment); incidence of serious hepatotoxicity: 14.0%
2. Diarrhea (mean time to occurrence 7.2 months); incidence of serious/severe diarrhea: 14.0%
3. Pneumonitis; incidence <5%
4. Neutropenia: Grade 3 or 4 neutropenia occurs in approximately 31% of patients receiving the 150mg bid dose.
5. CYP3A affects: CYP3A inducers can reduce the AUC of idelalisib by 75%; CYP3A inhibitors can increase the AUC of idelalisib by 1.8 fold; idelalisib is strong CYP3A inhibitor.
6. Increase risk of developing PCP
7. CMV viremia

8.2. RISK MINIMIZATION

Patients will have comprehensive metabolic panels performed every 14 days through day +180 , then monthly through day +270.

Patients undergoing allo BMT may develop intestinal aGVHD which may present with diarrhea or ileus. All patients with >3 grade diarrhea will also be evaluated for aGVHD in addition to idelalisib dose modification.

Patients undergoing allo BMT often develop late neutropenia after achieving neutrophil recovery. To help limit the depth of neutropenia that could be attributable idelalisib, idelalisib will be dosed at 100mg bid, the

suggested dose reduction for patients experiencing an ANC <.5Gi/L while on the standard 150mg bid dosing schedule

CYP3A interactions. Commonly, patients undergoing allo BMT require azole based antifungal prophylaxis and/or treatment. Patients receiving posaconazole or voriconazole will have these levels checked every 14 days while receiving idelalisib.

In the post allo BMT patient population, novel toxicities need to be considered: Non T-cell engraftment and acute GVHD. Stopping rules, as defined in section 6.0 will be followed to stop this study, if compared to placebo l controls, the differential in incidence of toxicities of any kind between the idelalisib group and the placebo control group is >10%.

CMV viremia: CMV serum PCR analysis every 14 days between days 90-and day +120, then monthly through day +270: treat according to BMT policy guidelines.

PCP: continue BMT policy guidelines of PCP primary prophylaxis for at least through the time of active-study participation.

9. Adverse Events

9.1. Overview

The Principal Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE (adverse event) or SAE (serious adverse event) as described in this protocol. All AEs and SAEs will be recorded in the source documents and on the appropriate electronic CRF(s). All data will be reviewed periodically by the SKCCC Safety Monitoring Committee (SMC), which may provide recommendations about withdrawing any participant and/or terminating the study because of safety concerns.

Adverse events that are classified as serious according to the definition of health authorities must be reported promptly and appropriately to the Principal Investigators in the trial, IRBs and health authorities. This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording and reporting them. Information in this section complies with *21CFR 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH Guideline E-6: Guidelines for Good Clinical Practice*; and applies the standards set forth in the National Cancer Institute (NCI), *Common Terminology Criteria for Adverse Events, Version 4.0 (May 28, 2009)*.

9.2. Definitions

9.2.1 Adverse Events

An AE is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial. An AE for participants will be followed until it resolves or until 30 days after the participant terminates from the study, whichever comes first. All AEs will be reported as specified in sections 9.2.2 and 9.2.3. **Error! Reference source not found.** Whether they are or are not related to disease progression or study participation.

9.2.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

9.2.3 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or SAR is considered "serious" if, in the view of the Investigator, it results in any of the following outcomes:

- Death: A death that occurs during the study or that comes to the attention of the Principal Investigator during the protocol-defined follow-up period as defined in section 4.0 must be reported whether it is considered treatment-related or not.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of the Investigator, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.2.4 Unexpected Adverse Events

A SAR is considered "unexpected" if it is not identified in the package insert and/or drug label, or protocol, or is not listed at the specificity, or severity that has been observed (21 CFR 312.32(a)).

9.3. Collecting and Recording Adverse Events

9.3.1 Methods of Collection

Adverse events for recipients will be collected from the time the participant receives the first dose of study medication as specified in section 9.4. Adverse events will be followed until the time an event is resolved or until 30 days after the recipient completes or terminates from the study, whichever comes first. The methods for collecting AEs will include:

- Observing the participant.
- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

An abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) can also indicate an AE if it is determined by the Investigator to be clinically significant. If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

9.3.2 Severity of Adverse Events to be collected

All AE grades will be defined per NCI-CTCAE version 4.0 criteria unless otherwise specified starting at the beginning of Idelalisib treatment

With the following exceptions, all AEs of grade 3 or higher will be collected from the time at which the participant receives the first dose of study medication as specified in section 9.4until the time the participant completes or prematurely withdraws from the study:

- Haematological abnormalities will be collected as AEs per NCI-CTCAE v. 4.0 criteria once participants have achieved platelet and neutrophil recovery.
- All episodes of allograft failure and of acute, grade III or IV GVHD will be collected as AEs.

9.4. GRADING AND ATTRIBUTION OF ADVERSE EVENTS

9.4.1 Grading Criteria

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's ***Common Terminology Criteria for Adverse Events Version 4.0*** (published May 28, 2009). This document (referred to herein as the "NCI-CTCAE v. 4.0 manual") provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs.

Severity of adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE v. 4.0 manual:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

For additional information and a printable version of the NCI-CTCAE v. 4.0 manual, go to http://ctep.cancer.gov/reporting/ctc.html

ATTRIBUTION DEFINITIONS

Adverse events will be categorized for their relation to one or more of the following:

- bone marrow transplantation
- investigational study medication, Idelalisib
- other protocol-directed study procedures

The Principal Investigator will do the initial determination of the relation, or attribution, of an AE to study participation and will record the initial determination on the appropriate eCRF and/or SAE reporting form. The relation of an AE to study participation will be determined using definitions in Table 1.

TABLE 1: ATTRIBUTION OF ADVERSE EVENTS

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy)
Unrelated Categories		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.

9.5. Reporting Serious Adverse Events

Serious adverse events must be reported to the Johns Hopkins University IRB within 48 hours of occurrence

10. Ethical, Regulatory, and Administrative Considerations

10.1. Statement of Compliance

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines—adopting the principles of the Declaration of Helsinki—and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by the sponsor and an appropriate ethics review committee or institutional review board (IRB). Any amendments to the protocol or consent materials must also be approved by the Sponsor, the IRB and submitted to FDA before they are implemented.

10.2. Informed Consent

The principles of informed consent are described in the Code of Federal Regulations 21 CFR, part 50.

Participants or their legal guardians must be made aware of the investigational nature of this treatment protocol, and have the possible risks, hazards and benefits of the protocol explained to them. The information that is given shall be in a language understandable to the participant. No informed consent, whether oral or written, may include any exculpatory language through which the patient is made to waive or appear to waive any of their legal rights, or releases or appears to release the Principal Investigator, the institution, or its agents from liability for negligence.

The participant, or legal guardian, must be able to comprehend the informed consent and must sign the document prior to registration on study. This will occur between Day +60 after HSCT and Day +100. A copy of the informed consent will be given to a prospective participant for review. The attending physician, in the presence of a witness, will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason. The participant will receive a copy of the respective signed consent form.

10.3. PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant's name, will be used to collect, store, and report participant information.

10.4. INSTITUTIONAL REVIEW

The principles of Institutional Review Board (IRB) are described in the Code of Federal Regulations 21 CFR, part 56.

The Principal Investigator will obtain approval for the study from the IRB. The Principal Investigator must notify the IRB within 5 days of protocol deviations in emergency situations regarding patient safety. The Principal Investigator will be responsible for obtaining annual IRB renewal through the duration of the study, or more frequently if required by the IRB. Copies of the Principal Investigator's report and copies of the IRB's continuance of approval must be maintained in the regulatory binder located at the clinical site.

10.5. MONITORING PLAN

This is a DSMP Level II study under the SKCCC Data Safety Monitoring Plan (12/6/2012). Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by the Principal Investigator and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

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12. APPENDIX 1-4

Appendix 1: **Staging and grading of acute graft-versus-host disease**

1. Staging: Record the highest level of organ abnormalities during the assessment period: Use the "rule of 9s" to compute percentage of body surface area for the skin assessment.
   a. Skin
      Stage I: Maculopapular rash < 25% of body surface
      Stage II: Maculopapular rash 25-50% of body surface
      Stage III: Generalized erythroderma (>50% of body surface)
      Stage IV: Generalized erythroderma with bullous formations and desquamation
   b. Intestinal Tract
      Stage I > 500 ml/day
      Stage II > 1000 ml/day
      Stage III > 1500 ml/day
      Stage IV > Severe abdominal pain, with or without ileus
   c. Liver
      Stage I: Bilirubin 2-3 mg/dL
      Stage II: Bilirubin 3-6 mg/dL
      Stage III: Bilirubin 6-15 mg/dL
      Stage IV: Bilirubin > 15 mg/dL

2. Overall Clinical Grading of Severity of Acute GVHD:
   Grade I: Stage 1-2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance
   Grade II: Stage 1-3 rash; stage 1 gut involvement, or stage 1 liver involvement (or both); mild decrease in clinical performance
   Grade III-Stage 2-3 skin rash; 2-3 gut involvement or stage 2-4 liver involvement (or both); marked decrease in clinical performance
   Grade IV-Similar to Grade III with stage 2-4 organ involvement and extreme decrease in clinical performance

Appendix 2: Study Calendar and Schema

12.1. STUDY CALENDAR

	Screening and Baseline (	Cycle 1, Day 1 Day +90 (± 10 Days)	Cycle 1, Day 15	Cycles 2-6 Day 1 (+/- 7 days)	30 days Post last dose	Month 12 (± 14 Days)
Informed Consent[a]	Days 60 -100					
Medical History	X					
Physical Exam	X	X		X	X	X
AE Assessment	X	X		X	X	X
CBC with diff	X	X	X	X	X	X
Comprehensive metabolic panel e (CMP) [b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
PT, PTT, INR	X					
Serum β-HCG (if applicable)	X					
CMV PCR[d]	X[d]	X	X	X		
Idelalisib		X		X		
Standard of care per institution						
T-cell chimerism	X					X
Bone marrow biopsy (as std of care)	X					X
aGVHD/cGVHD assessments	X	X	X	X		X
Correlative studies[c]	X	X		X[c]		X

[a]Informed consent will be collected beginning on Day +60 after BMT until Day +100.

[b] CMP to include BUN, creatinine, sodium, potassium, chloride, AST, ALT, total bilirubin, alkaline phosphatase.

[c] Additionally specimens should be obtained from peripheral blood and bone marrow collections as a part of routine clinical care such as GVHD, toxicity and/or disease relapse Correlative peripheral blood samples should be collected on Day 1 of every other cycle beginning with Cycle 2

[d]Cytomegalovirus (CMV) viral load assay will be monitored by PCR every 14 days between days +90-and day +120, then monthly through day +270: treat according to BMT policy guidelines.

Appendix 3: Performance Status Scales

ECOG PERFORMANCE STATUS SCALE GRADE DESCRIPTION

0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activities and able to carry out work of a light or sedentary nature, e.g. light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

KARNOFSKY PERFORMANCE STATUS SCALE

100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease. Able to carry on normal activity and to work; no special care needed.
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.
60	Requires occasional assistance, but is able to care for most of his personal needs. Unable to work; able to live at home and care for most personal needs; varying amount ofassistance needed.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly. Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
0	Dead

Appendix 4: Counterindicated Medications

CYP3A affects: CYP3A inducers can reduce the AUC of idelalisib by 75%; CYP3A inhibitors can increase the AUC of idelalisib by 1.8 fold; idelalisib is strong CYP3A inhibitor. Importantly, with direct relevance to this study is the lack of data supporting strong interaction with voriconazole. Azoles are often the medication of choice for patients with suspect fungal or anti-bacterial non-responsive fevers during alloBMT. The elimination of idelalisib is predominantly mediated by the hepatic pathway. Idelalisib is primarily metabolized by aldehyde oxidase with a lesser involvement of cytochrome P450. The major metabolite of idelalisib is GS-563117. Data indicate that CYP3A inhibition by concurrent use of azoles may result in modestly higher exposures of idelalisib, but the change is not of clinical relevance[21]. In this study, as the dosing of idelalisib is already reduced to 100mg bid to provide additional risk mitigation. Additionally, patient's receiving azole therapy while on idelalisib will have serum levels monitored to adjust to target levels

List of prohibited inhibitors and inducers of isoenzyme CYP3A

INDUCERS
Strong inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) **Moderate inducers:** bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir **Weak inducers:** amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine
INHIBITORS
Strong Inhibitors: Boceprevir,clarithromycin, conivaptan,grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir,mibefradil, nefazodone, nelfinavir,posaconazole, ritonavir, saquinavir, telaprevir,telithromycin,voriconazole **Moderate inhibitors:** Amprenavir, aprepitant,atazanavir, ciprofloxacin,darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, imatinib, verapamil **Weak inhibitors:** Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine,

cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal,isoniazid, nilotinib,oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

CLINICALLY RELEVANT DRUG INTERACTIONS MEDIATED BY PGP

PgP Substrates	PgP Inhibitors and PgP/CYP3A Dual Inhibitors	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel, talinolol, everolimus	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, (GF120918), fexofenadine, fluvoxamine, ginko (ginko biloba), indinavir, itraconazole, lopinavir, (LY335979), mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, (PSC833), paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinesis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan valspodar, verapamil	rifampin, St John's wort