# Open Label Phase II Study of Ixazomib for the Prevention of Recurrent or Late Acute and Chronic Graft-versus-Host Disease at 1-year after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Hematologic Malignancies

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program**.

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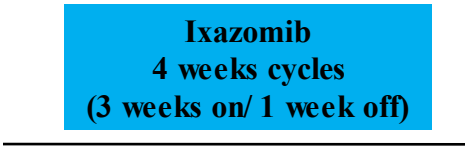
## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single arm open label phase 2 study evaluating the potential effect of ixazomib on the prevention of recurrent or late acute graft-versus-host disease (GVHD) and chronic GVHD at 1-year following reduced intensity (RI) or non-myeloablative (NMA) allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of hematologic malignancies. Patients will be eligible for enrollment if they are without active acute or chronic GVHD between days +100 and +150 following HSCT. After enrollment patients will initiate treatment with ixazomib and continue until all immunosuppressants are tapered off or 1 year post-HSCT is reached (whichever occurs first) or grade II-IV acute and/or chronic GVHD develops or malignant disease relapse/ progression occurs. The primary aim is to assess the incidence of development of grade II-IV recurrent or late acute GVHD (aGVHD) and chronic GVHD (cGVHD) at 1-year following ixazomib administration post-HSCT. Calcineurin inhibitor based drug and methotrexate (MTX) will be used for initial GVHD prophylaxis. Ixazomib will be used as secondary GVHD prophylaxis as above.

Patients will be monitored post-transplant for incidence and severity of recurrent or late acute and cGVHD at 1-year post-HSCT, transplant-related mortality (TRM), characteristics of immune recovery, as well as overall and event-free survival.

**Protocol Schema**




Ixazomib 4 mg PO once a week. Cycles are every 28 days (3 weeks on/ 1 week off) until discontinuation of immunosuppressants or 1 year post-HSCT (whichever occurs first), or grade II-IV acute or chronic GVHD develops or malignant disease relapse/ progression occurs.

## 2.1 OBJECTIVES AND SCIENTIFIC AIMS

**The primary aim** is to assess the efficacy of ixazomib for the prevention of recurrent or late grade II-IVa GVHD or chronic GVHD at 1 year post-transplant.

**Secondary objectives include**:

- the incidence of overall and moderate/severe cGVHD.
- the incidence of transplant-related mortality (TRM).
- the incidence of disease progression.
- the incidence of grade II-IV and III-IV acute GVHD
- the probabilities of overall and progression-free survival after HSCT.

- proportion of subjects with discontinuation of immunosuppressive medication after HSCT.
- Characteristics of immune reconstitution

**Exploratory objectives include**:

- Describe the percentage of patients who get vaccines on time and percentage of patients who do not respond to vaccines.
- Describe treatment failure for patients who enroll on post-transplant day +100 to +125 and for patients who enroll on post-transplant day +125 to +150.

**Safety endpoints**:

- Incidence and severity of adverse events (AEs) and serious AEs (SAEs).

## 3.0 BACKGROUND AND RATIONALE

GVHD is a frequent and at times unpredictable severe complication of HSCT[1-3], and is a leading cause of TRM following HSCT[1,4]. GVHD can be characterized as acute or chronic, based on the clinical manifestation[5]. Acute GVHD damages the skin, gut, and/or liver. Nausea, vomiting, abdominal pain, diarrhea, bloody stool and/or jaundice are commonly present. While calcineurin-inhibitor based GVHD prophylaxis has decreased the incidence and mortality associated with aGVHD, it provides inadequate protection since this disease commonly affects > 50% of HSCT recipients[6]. Risk factors associated with aGVHD include recipients of sex-mismatched HSCT and/or HLA-mismatched donor, peripheral blood stem cell graft and myeloablative conditioning[7,8]. The incorporation of an additional prophylactic agent could potentially decrease the incidence of GVHD development and ameliorate transplant complications including TRM. However, in RI and NMA conditioning transplantation, critically dependent of graft-versus-tumor effect for cure, *in vivo* T-cell antibody based GVHD prophylaxis (i.e. anti-thymocyte globulin) can also impair survival[9]. Thus, novel T-cell replete GVHD regimens would be of considerable utility.

For the patients who develop grade II-IV aGVHD, the standard first-line treatment is oral or IV corticosteroids[10]. It is difficult to predict at the onset of aGVHD who will respond fully or partially, or who will be refractory. Approximately 50% of patients will not achieve a sustained complete response of aGVHD to first-line therapy with corticosteroids[6]. For those patients who fail to respond to corticosteroids additional immunosuppressive agents are necessary[11,12]. Unfortunately, survival is poor in steroid-resistant aGVHD at approximately 15% at 2 years[13].

Acute GVHD may develop after day 100. Recurrent aGVHD is defined as recurrence of clinical findings of aGVHD after day 100 whereas late aGVHD is non-chronic GVHD features occurring after 100 days post transplant[5]. The former, occurs more often after transplants that utilize RI and NMA[14]. Chronic GVHD is diagnosed based on established criteria outlined at the NIH consensus conference[5]. In general, cGVHD is characterized to varying degrees by sclerosis of lacrimal and salivary ducts, scleroderma-like changes of the skin, chronic inflammation and scarring of the gastrointestinal tract with consequent malabsorption and diarrhea, inflammation of the liver, suppression of the immune system and occasionally other auto-immune phenomena (such as, auto-immune hemolysis) or involvement of other organs (such as, pulmonary involvement). Chronic GVHD is diagnosed and graded as mild,

moderate or severe[5]. While patients with moderate or severe manifestation generally need systemic therapy, usually including corticosteroids, the treatment of cGVHD can change based on organ system involvement. While reducing the intensity of the preparative regimen has decreased the incidence of early presentations of aGVHD, the incidence of cGVHD has not been affected by this change of practice[14,15].

### 3.1 Graft-versus-host Disease after Reduced Intensity and Non-Myeloablative Transplantation

The Center for International Blood and Marrow Transplant Research evaluated the outcomes of 1676 patients who underwent allogeneic HSCT after RI conditioning[9]. They found that patients who received a T-cell replete regimen had a 3-year incidence of cGVHD of 52% (95%CI: 49-56) whereas patients who had alemtuzumab-containing and ATG-containing regimens had a lower incidence of 24% (95%CI: 18-30) and 40% (95%CI: 36-44), respectively, p = <0.001. However, the risk of 3-year relapse was lower in the T-cell replete regimen when compared to alemtuzumab-containing and ATG-containing regimens (38% vs 51% vs 49%). Similarly, disease-free survival was higher in the T-cell replete regimen than those who received *in vivo* T-cell depleted regimens.

Mielcarek et al analyzed GVHD according to conditioning regimen intensity in 96 allograft recipients[14]. The incidence of grade II-IV aGVHD at day 100 was higher in the myeloablative conditioning recipients of 77% when compared to that of 62% in NMA conditioning recipients (p = 0.02) whereas grade III-IV severe aGVHD was similar (p = 0.89) This comparison revealed that the median time to initiation of corticosteroids for treatment of GVHD was delayed by more than 2 months (median time 3.0 months) in the NMA group when compared to the myeloablative recipients (median time 0.95 months). These findings suggest that the median onset of GVHD is delayed in NMA conditioning recipients. The probability of cGVHD was similar among for recipients of NMA and myeloablative conditioning (77% vs 74%, p = 0.37).

Ceberio et al evaluated 71 patients with hematologic malignancies who received either reduced RI (n = 12) or NMA (n = 59) conditioning followed by allogeneic HSCT[15]. GVHD prophylaxis consisted of sirolimus, tacrolimus and low-dose methotrexate. The analysis showed a cumulative incidence of grade II-IV and III-IV aGVHD at 1 year of 28% (95%CI: 18-39) and 7% (95% CI: 3-15), respectively. The median onset of aGVHD was day 123 (range 17-268) and the majority of the patients who developed aGVHD occurred in the context of immunosuppression tapering. The cumulative incidence of chronic GVHD in 70 evaluable patients at 1 year was 15% (95% CI: 8-24) and 2 years was 32% (95%CI: 22-44).

The results of a prospective phase II trial assessing peri-transplant rituximab with a NMA conditioning regimen for patients with CD20 B cell NHL was recently published by Sauter et al from the adult transplantation group at Memorial Sloan Kettering Cancer Center[16]. The data from this study (n = 51) reveals a promising 2-year event-free survival (EFS) in this group of patients; the EFS was 84% and 40% for chemosensitive as compared to chemotherapy refractory patients before allo-HSCT. The cumulative incidence of grade II-IV aGVHD at 3 and 6 months after HSCT was 18% (95%CI: 7-29) and 25% (95%CI: 13-38), respectively, whereas the cumulative incidence of severe grade III-IV aGVHD at 3 and 6 months was 8% (95%CI: 0-16) and 11% (95%CI: 3-24), respectively. The cumulative

incidence of moderate to severe cGVHD at 1 year was 14% (95%CI: 3-24) and at 2 years was 29% (95%CI: 15-44). Notable, GVHD was noted to be a more frequent cause of death than disease relapse or progression. The number of patients who suffered a transplant-related event (most of which were due to GVHD) was 20 (19%), while the number of patients who relapsed or progressed was 14 (13%). In particular, in those patients with FL, there was one disease-related event and 9 transplant-related events. In a follow-up analysis as of September 1, 2014, 46 patients were alive without progression of disease at day 100. Of those, the development of any GVHD syndrome was assessed. This analysis demonstrated a cumulative incidence of 63% (95%CI: 47-76) at 1-year of any GVHD syndrome. Thirty-five percent (n = 16) had no active GVHD whereas 30 patients had active GVHD syndrome. The predominant manifestation was late onset aGVHD (n = 9, 19.5%) and overlap syndrome (n = 9, 19.5%), followed by classical chronic GVHD (3 interrupted, 4 de novo) and recurrent aGVHD (n = 5, 11%) (unpublished data).

### 3.2 Proteosome inhibitors to reduce GVHD

The proteasome inhibitor, bortezomib, has immunomodulatory properties with the ability to selectively deplete proliferating alloreactive T lymphocytes, reduce T-helper type 1 cytokines, and block antigen presenting cell activation[17,18]. Bortezomib may also spare regulatory T-cells (Treg) that may be relevant in GVHD control. In a phase I/II trial at Dana Farber Cancer Institute[19], Koreth el al evaluated Bortezomib-based regimen for the prophylaxis against GVHD for patients who received HLA-mismatched unrelated donor transplant after RI conditioning regimen. GVHD prophylaxis consisted of tacrolimus, methotrexate and Bortezomib. A total of 45 patients were enrolled on this trial in which bortezomib was given on days +1, +4, and +7. Toxicities included cytopenias and infections, not deemed to be related to the study drug. The cumulative incidence of grade II-IV aGVHD at 180 days was 22% whereas the cumulative incidence of cGVHD at 12 months was 29%. Additionally, the cumulative incidence of non-relapse mortality at 2 years was 11%. Given these results, the authors surmised that bortezomib is a promising novel immune modulatory agent that may decrease GVHD following allo-HSCT.

The effect of Bortezomib on cGVHD was also assessed in a murine model[20]. This study demonstrated that Bortezomib ameliorated cGVHD cutaneous lesions, which were also associated with a reduction in total numbers of germinal center B cells and lower B-cell activating factor gene expression levels in cutaneous lesions. Pai et al conducted a dose escalation clinical trial in patients with steroid-intolerant, dependent or resistant[20]. Ten patients received Bortezomib, of those, 6 received >60% of the scheduled doses and 5 of 6 patients responded to therapy, achieving a marked clinical improvement, which was also associated with reductions of peripheral B cells and minimal toxicity. In the majority of the responders, the dose and/or number of immunosuppressive drug therapies were reduced during treatment with Bortezomib.

#### 3.2.1 Ixazomib

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory multiple myeloma (MM), and relapsed or refractory light-chain (AL) amyloidosis. In addition, ongoing clinical

pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib are ongoing. Preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated.

Targeting T cells alone has yielded limited success in the prevention of GVHD following allogeneic HSCT. Dendritic cells play a role in alloreactivity and therefore, represent a suitable target. Proteasome inhibitors have the ability to inhibit the function and maturation of dendritic cells, which have prompted investigators to evaluate their potential role in the prevention of GVHD. Ixazomib is the first oral proteasome inhibitor that dissociates rapidly from 20S proteasome, and therefore, is truly reversible. Ixazomib has demonstrated immune modulatory effects, inhibition of maturation and function of dendritic cells, inhibition of pro-inflammatory cytokines production in dendritic cells, and inhibition of T-cell proliferation. These effects suggest a potential role of this drug in the prevention of acute and chronic GVHD. While proteasome inhibitor bortezomib has demonstrated efficacy in the prophylaxis and treatment of GVHD, its administration by intravenous or subcutaneous route require frequent hospital visits and monitoring which can limit its use in the outpatient setting. Ixazomib may overcome this limitation since is orally bioavailable and is associated with favorable safety and toxicity profile.

#### 3.2.1.1 Pharmacokinetics and drug metabolism

Clinical intravenous and oral PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (Tmax) of approximately 0.5 to 2.0 hours and a terminal disposition half-life (t1/2) after multiple dosing of approximately 5 to 7 days[21]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA[22]. Therefore, fixed dosing was recommended in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). *In vitro* studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP

inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole[23]. This resulted in the exclusion of concurrent use of strong CYP3A4 inhibitors proteasome inhibitor/ ixazomib.

### 3.2.1.2. Ixazomib safety profile

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral studies (47%). Other common AEs reported in the pooled intravenous and oral safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythema; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%) (Table 3.2.1.2).

The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

**Table 3.2.1.2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies**

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total<br>n = 201<br>n (%) |
|---|---|
| Subjects with at Least One Adverse Event | 197 (98) |
| Gastrointestinal disorders | 160 (80) |
| Nausea | 106 (53) |
| Diarrhea | 88 (44) |
| Vomiting | 77 (38) |
| Constipation | 46 (23) |
| Abdominal pain | 33 (16) |
| General disorders and administration site conditions | 151 (75) |
| Fatigue | 103 (51) |
| Pyrexia | 51 (25) |
| Oedema peripheral | 27 (13) |
| Asthenia | 31 (15) |
| Nervous system disorders | 92 (46) |
| Headache | 29 (14) |
| Dizziness | 26 (13) |
| Neuropathy peripheral | 21 (10) |
| Metabolism and nutrition disorders | 107 (53) |
| Decreased appetite | 64 (32) |
| Dehydration | 37 (18) |
| Blood and lymphatic system disorders | 98 (49) |
| Thrombocytopenia | 68 (34) |

**Table 3.2.1.2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies**

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total<br>n = 201<br>n (%) |
|---|---|
| Anaemia | 42 (21) |
| Neutropenia | 29 (14) |
| Lymphopenia | 20 (10) |
| Skin and subcutaneous tissue disorders | 90 (45) |
| Rash macular[a] | 23 (11) |
| Musculoskeletal and connective tissue disorders | 93 (46) |
| Back pain | 24 (12) |
| Arthralgia | 28 (14) |
| Respiratory, thoracic and mediastinal disorders | 78 (39) |
| Cough | 28 (14) |
| Dyspnea | 30 (15) |
| Infections and infestations | 89 (44) |
| Upper respiratory tract infection | 31 (15) |

*Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.*

*Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.*

*a Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.*

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied including non-Hodgkin's disease and Hodgkin's disease[24].

### 3.3 Summary

GVHD is frequent after HSCT and is a major cause of TRM. Previous analyses of patients with hematologic malignancies treated with RI or NMA conditioning followed by HSCT reveal that GVHD usually develops after day 100 and particularly during immunosuppression tapering. Thus, using another agent for the prevention of GVHD after day 100 could potentially decrease the incidence and ameliorate GVHD-related mortality. Additionally, past experience with proteasome inhibitors to reduce GVHD supports further investigation of these agents. As such, the use of ixazomib, which is an oral proteasome inhibitor with

minimal neurotoxicity, is an optimal candidate to add in this setting in an effort to prophylactically decrease GVHD development.

The primary aim of this study is to assess the efficacy of ixazomib for the prevention of recurrent or late acute grade II-IV GVHD or chronic GVHD at 1-year post-transplant. We will administer ixazomib starting within days 100 to 150 after HSCT. This window has been chosen so as to allow count recovery post-transplant prior to starting an agent that may cause cytopenias. This study drug will be added to our standard approach for the prevention of GVHD. Patients will have received a RI or NMA conditioning for the treatment of their myeloid or lymphoid hematologic malignancy, followed by an 8/8 or 7/8 HLA-matched volunteer donor HSCT, and the combination of calcineurin inhibitor based drug (either tacrolimus or cyclosporin) and methotrexate for GVHD prophylaxis. Given that ixazomib is an oral proteasome inhibitor that is given once weekly, this additional agent to the post-transplant treatment regimen will be convenient for patients. After enrollment, patients will initiate treatment with ixazomib and continue until all immunosuppressants are tapered off or 1 year post-HSCT (whichever occurs first), or grade II-IV acute or chronic GVHD develops or malignant disease relapse/ progression occurs.

## 4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.2 Design

This is a single arm phase 2 study to evaluate a post-transplant proteasome inhibitor, ixazomib, as prophylaxis against recurrent or late acute and chronic GVHD. Ixazomib will be initiated within days 100 to 150 post-transplant in patient's $\geq$ 18 years-old with either myeloid or lymphoid hematologic malignancy treated with a RI or NMA HSCT and will have received calcineurin inhibitor based drug (tacrolimus or cyclosporin) and methotrexate as part of their initial GVHD prophylaxis.

### 4.3 Intervention

The primary aim is to assess the efficacy of ixazomib for the prevention of recurrent or late grade II-IV aGVHD or chronic GVHD at 1-year post-transplant. The accrual period will be approximately 3 years with an additional 12 months of follow-up after the accrual period has been completed. Stopping rules are in place for secondary graft failure without autologous recovery and excessive treatment related toxicity. The target sample size for this study is 46 patients with an approximate accrual of 16 patients per year.

## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

If appropriate describe packaging, labeling and storage requirements of the agents and/or device(s). Indicate any special instructions for maintaining, tracking and monitoring that is required by sponsor, FDA and/or MSKCC.

### 5.1 MLN 9708 (Ixazomib)

Supplied as: strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The study drug will be supplied by Takeda Pharmaceuticals/ Millennium

as capsules of 0.2-, 0.5-, and 2.0 mg, or as capsules of 2.3-, 3.0- and 4.0 mg ixazomib. This is dependent on available ixazomib formulation.

Reconstitution directions: N/A.

Storage and stability: on receipt at the investigative site, study drug should remain in the blister and carton provided until use or dispensation. The container should be stored refrigerated (36°F to 46°F, 2°C to 8°C). All excursions should be brought to the sponsor's attention for assessment and authorization for continued use. Ensure that the drug is used before the retest expiry date provided by Takeda Pharmaceuticals/ Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Study drug dispensed to the patient for take-home dosing should remain in the listed packaging and carton and refrigerated as noted above until the point of use. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty carton to the investigative site, rather than discarding them.

Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported and dealt with on a case-by-case basis.

Preparation: Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water.

Clinical considerations: Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Hydration: A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Toxicities: see section 11.0

Incompatibilities: with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole), or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

## 6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

### 6.2 Subject Inclusion Criteria

Eligible patients will be consented by the Adult BMT service attending. All patients must meet all of the following inclusion criteria to be enrolled in the study:

All patients must meet all of the following inclusion criteria to be enrolled in the study:

- Patients 18 years or older.
- Diagnosis: myeloid or lymphoid hematologic malignancy treated with a RI or NMA conditioning HSCT who received calcineurin inhibitor based drug (for example: tacrolimus or cyclosporin) and methotrexate as part of their initial GVHD prophylaxis. Patients who received sirolimus as part of their GVHD prophylaxis will be eligible.
- Recipients of 8-7/8 HLA-matched donor. Post-HSCT period within day +100 to day +150.
- Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence and withdrawal are not acceptable methods of contraception).
- Male patients, even if surgically sterilized (i.e. Status post-vasectomy) must agree to one of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence and withdrawal are not acceptable methods of contraception).

Organ Function and Performance Status Criteria:

- Karnofsky score $\geq$ 70 %
- Absolute neutrophil count (ANC) $\geq$ 1000/mm$^3$ and platelet count $\geq$ 75,000/mm$^3$. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
- Calculated creatinine clearance $\geq$ 30 mL/min (based on the Cockcroft and Gault method)
- Total bilirubin $\leq$ 1.5 x upper limit of normal range (ULN).
- AST/ALT $\leq$ 3 x ULN (unless benign congenital hyperbilirubinemia).
- Hemoglobin $\geq$ 8.0 g/dL. Red blood cell transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.

## 6.3 Subject Exclusion Criteria

- Disease: evidence of progressive disease at the time of study enrollment.
- Prior Therapy: one or more prior allogeneic stem cell transplantation (prior autologous transplant is acceptable).
- Active acute or chronic GVHD.
- Active and uncontrolled infection.
- Pregnant or breast feeding.
- Major surgery within 14 days before enrollment.

- Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
- Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.
- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
- Patient or guardian unable to give informed consent or unable to comply with the treatment protocol including appropriate supportive care, follow-up and research tests.
- Patients with known allergy to boron or boron-containing products, or excipients in the various formulations of any agent.
- Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.
- Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
- Patient with $\geq$ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.
- Received post-transplant cyclophosphamide

## 7.0 RECRUITMENT PLAN

Patients who meet the eligibility criteria as listed in Section 6.0 will be recruited for this study by an Attending Physician of the Adult BMT service. This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations.

## 8.1 PRETREATMENT EVALUATION

### 8.1 Pretreatment evaluation

The following tests must be performed prior to study drug treatment starts. Tests that are performed within 30 days prior to consent are not required to be repeated:

- Complete history, review of systems, physical exam (including performance status)
- CBC with differential, comprehensive metabolic panel (CMP), thyroid function test (TSH and free T4)
- EKG
- Urinalysis
- Pregnancy test (required only for females of childbearing age)
- Immune function tests (testing is performed following institutional practice and is recommended before starting treatment with ixazomib)

## 9.1 TREATMENT/INTERVENTION PLAN

Patients will be cared and monitor according to he allogeneic BMT clinical care guidelines. https://one.mskcc.org/sites/pub/corp/bmt/Documents/H3_Allo%20Guidelines_01_27_2016.pdf Patients will have received a calcineurin inhibitor based GVHD prophylaxis with either tacrolimus or cyclosporin in combination with methotrexate. The study drug will be initiated between day 100 to 150 post-allograft.

Tapering of calcineurin inhibitor (CNI) will follow the institutional practice. For recipients of HLA-matched sibling donor, is recommended to initiate CNI taper around day 100 and taper at 10-25% decrements every 2 weeks. For recipients of HLA-matched unrelated and HLA-mismatched unrelated donors, is recommended to initiate CNI taper around day 180 and taper at 10-15% decrements in 4 weeks intervals.

## 9.2 GVHD prophylaxis

**Ixazomib** beginning between day +100 to +150 at a dose of 4 mg orally once per week (3 weeks on/ 1 week off). The patients will continue on this same dose until taper off from immunosupressants or 1 year post-HSCT is reached (whichever occurs first) or until the patient develops GVHD or malignant disease relapse/progression occurs. Patients who reach 1 year post-HSCT or discontinue immunosuppressants mid-cycle should complete their current cycle of ixazomib.

- The levels of the drug will not be monitored while the patients are on study.
- In order for patients to receive drug, they must have a platelet count > 75K, Hgb (untransfused) > 8 and an ANC > 1.0 (can be supported with G-CSF)
- If more than 2 doses in a row or more than 3 doses total are held, the patient is removed from study.
- Doses are given weekly +/- 3 days

### 9.1.1 Dose-modification guidelines

Treatment with ixazomib will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC $\geq$ 1,000/mm$^3$
- Platelet count $\geq$ 75,000/mm$^3$
- Serum creatinine ≤ 2.5 mg/dL and less than double from pre-treatment evaluation value

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the Principal Investigator.

Ixazomib dose adjustments:

| Dose Level | Dose (mg) |
|---|---|
| Starting Dose | 4.0 mg |
| -1 | 3.0 mg |
| -2 | 2.3 mg |

| | |
|---|---|
| -3 | Discontinue |

**Table 9.1.1 Ixazomib dose adjustments for hematologic toxicities**

| Criteria | Action |
|---|---|
| Within-Cycle Dose Modifications<br>• If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.50 \times 10^9$/L on ixazomib dosing day (other than Day 1)<br>• If serum creatinine > 2.5 mg/dL or has doubled from pre-treatment evaluation | • Ixazomib dose should be withheld.<br>• Complete blood count (CBC) with differential should be repeated until the ANC and/or platelet counts have exceeded the prespecified values.<br>• Upon recovery, ixazomib may be reinitiated with 1 dose level reduction. |
| Dose Modifications for Subsequent Treatment Cycles<br>• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 9.1.1<br>• ANC $< 1.0 \times 10^9$/L, platelet count $< 75 \times 10^9$/L, serum creatinine > 2.5 mg/dL, serum creatinine doubled from pre-treatment evaluation, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition | • Hold ixazomib until resolution as per criteria Section 9.1.1<br>• Upon recovery, reduce ixazomib 1 dose level.<br>• The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the PI. |
| Dose Modifications for Subsequent Treatment Cycles<br>• All hematologic toxicities | • For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle,:<br>o If dose was reduced within the cycle, start the next cycle at that same dose.<br>o If due to toxicity timing, i.e. after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle.<br>o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity. |

### 9.1.2. Excluded concomitant medications and procedures

The following medications and procedures are prohibited during the study.
Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. A DDI with a strong inhibitor would increase the ixazomib exposure and could lead to a higher probability of an AE:

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole.

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (rationale: Unlike with inhibitors, if there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital.
- Exclude foods and dietary supplements include St. John's wort and Ginkgo biloba.

The following procedures are prohibited during the study:

- The addition of immunosuppresant(s) and/or GVHD prophylactic agents once enrolled in the study.
- Platelet transfusions to help patient meet eligibility platelet level criteria are not allowed within 3 days prior to study drug dosing for any dosing day.

#### 9.1.3. Precautions and restrictions

Fluid deficit should be corrected before initiation of treatment and during treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced kidney injury in patients with decreased renal function.

### 9.2 Management of clinical events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 9.1.1

#### 9.2.1 Nausea and/or vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

#### 9..2.2 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. If GVHD is suspect, proper evaluation including endoscopic evaluation with biopsy should be conducted. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

### 9.2.3 Erythematous rash with or without pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted.

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g. using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

### 9.2.4 Neutropenia and thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 9.1.1). Therapy can be reinitiated at a reduced level upon recovery of neutropenia.

Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

### 9.2.5 Fluid deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

### 9.2.6 Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure, should be managed according to standard clinical practice, including considerations for dose adjustment of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study as needed during treatment to avoid dehydration.

### 9.2.7 Posterior reversible encephalopathy syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

### 9.2.8 Transverse myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that this drug may have contributed to transverse myelitis cannot be excluded.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

All patients will be closely monitored and evaluated as per MSKCC BMT standard of care guidelines. Study specific assessment schedule listed in table below.

Evaluation includes history and physical examination, blood count, chemistry including liver function test at screening, 6 months and 12 months post-allograft. Blood counts and blood chemistries will be monitored before the initiation of each treatment cycle and prior to the third dose of cycles 1 and 2.

Toxicity assessment will be performed monthly during the duration of treatment or discontinuation of the study drug. Prior to initiating the first two cycles, toxicity assessments will be performed at MSKCC's main campus when feasible. Toxicity assessments for subsequent cycles can be collected via phone call.

Acute and chronic GVHD will be diagnosed and graded according to established criteria[5,25]. Assessments will be obtained at approximately at day 100, 6 months, and 12 months. Additional time points will be done if clinically indicated.

**Scheduled Study Assessments:**

| | Study time-points | | | | | |
|---|---|---|---|---|---|---|
| **Procedures** | **Consent** | **Pre-Treatment Evaluation** | **Ixazomib Cycles 1-9** | **6 months post-HSCT** | **12 months post-HSCT** | **Safety Follow Up** |
| Window | 100 – 150 days post-HSCT | - 30 days prior to Dose 1 | +/- 3 days | +/- 14 days | +/- 30 days | 30 days after last treatment +/- 7 days |
| Informed consent | X | | | | | |
| History/ Physical | | X | | X | X | |
| Karnofsky score | | X | | | | |
| CBC[1] | | X | X | | | |
| Blood Chemistry/ CMP[1] | | X | X | X | X | |
| Thyroid function test[2] | | X | | X | X | |
| EKG | | X | | | | |
| Pregnancy test (if applicable) | | X | | | | |
| Urinalysis | | X | | | | |
| Immune function testing[3] | | X | | X | X | |
| GVHD evaluation | X | | | X | X | |
| Toxicity assessment[4] | | X | X | X | X | X |

[1] CBC and Chemistry are required prior to dose 1 and dose 3 for the first 2 cycles and then prior to first dose of each subsequent drug cycle
[2] Thyroid function test should include thyroid stimulating hormone (TSH) and free T4
[3] Immune function testing is performed per institutional practice and is recommended at indicated study time points.
[4] To be collected prior to first dose of each cycle.

## 11.0 TOXICITIES/SIDE EFFECTS

### 11.1 Toxicity Grading

Toxicities will be graded on a scale of 0 to 4 as described by the NCI- Common Terminology for Adverse Events (CTCAE), version 4.0.

### 11.2 Ixazomib

Ixazomib may cause fatigue, thrombocytopenia, nausea, vomiting, diarrhea, decreased appetite. Less frequently the drug can cause rash, peripheral edema, and neutropenia. Further details of management of ixazomib-related hematologic toxicity AEs are described in Section 9.1.1.

Treatment modifications due to ixazomib-related AEs are outlined in Table 11.2.

**Table 11.2 Ixazomib treatment modification (delays, reductions, and discontinuations) due to adverse events (non-hematologic toxicities)**

| Adverse Event (Severity) | Action on Study Drug | CTCAE Description |
|---|---|---|
| **Peripheral Sensory Neuropathy:** Grade 1 peripheral sensory neuropathy | • No action | Grade 1: Asymptomatic; loss of deep tendon reflexes or paresthesia |
| Grade 2 peripheral sensory neuropathy | • Hold study drug until resolution to Grade ≤ 1 or baseline<br>• Once recovered, resume study drug at same dose | Grade 2: Moderate symptoms; limiting instrumental ADL |
| Grade 3 peripheral sensory neuropathy | • Hold study drug until resolution to Grade ≤ 1 or baseline<br>• Reduce study drug to next lower dose upon recovery | Grade 3: Severe symptoms; limiting self care ADL |
| Grade 4 peripheral sensory neuropathy | • Discontinue study drug | Grade 4: Life-threatening consequences; urgent intervention indicated |
| **Nervous System Disorder:** Grade 1 nervous system toxicity judged to be related to study drug | • No action | Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Grade 2 nervous system toxicity judged to be related to study drug | • Hold study drug until resolution to Grade ≤ 1 or baseline | Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL |
| New or worsening grade 2 or grade 3 or 4 toxicity judged to be related to study drug | • Discontinue study drug | Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL |

**Table 11.2 Ixazomib treatment modification (delays, reductions, and discontinuations) due to adverse events (non-hematologic toxicities)**

| Adverse Event (Severity) | Action on Study Drug | CTCAE Description |
|---|---|---|
| | | Grade 4: Life-threatening consequences; urgent intervention indicated |
| Grade 2 Rash | • Symptomatic recommendations. The investigator and project clinician may discuss considerations for dose modifications and symptom management. | Grade 2: Rash covering 10-30% BSA with or without symptoms; limiting instrumental ADL |
| Grade ≥ 3 nonhematologic toxicity judged to be related to study drug | • Hold study drug until resolution to Grade ≤ 1 or baseline<br>• Reduce study drug to next lower dose upon recovery | |
| If not recovered to Grade ≤ 1 or baseline within 4 weeks | • Discontinue treatment | |

## 12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

### 12.2 Criteria for therapeutic response for the primary endpoint

The primary aim is to assess the efficacy of ixazomib for the prevention of recurrent or late grade II-IV aGVHD or chronic GVHD by 1-year post-transplant. Therapeutic response will be determined by the absence of grade II-IV aGVHD or chronic GVHD diagnostic features (or any of the other failure criteria listed in 12.2) during the study window

Patients who receive at least one cycle of therapy will be considered evaluable for the primary endpoint.

### 12.3 Criteria for treatment failure for the primary endpoint

- Study drug is discontinued and unable to resume due to drug related toxicity.
- New onset or recurrence of grade II-IV aGVHD (including GVHD flares).
- New onset of chronic GVHD.
- Administration of systemic therapy for treatment of GVHD.
- Development of secondary graft failure during the administration of the study drug.
- Mortality (transplant or treatment-related)

If treatment failure criteria is met, the patient will be removed from the study. A 30-day follow-up will be conducted for end-of-treatment evaluation for toxicity assessment. This follow-up may be conducted via phone call or in-person by the clinical team.

## 12.4 Outcome assessment

### 12.3.1 Graft-versus-host disease (GVHD)

Acute GVHD will be diagnosed clinically and histological assessment will be obtained where possible. Grading of aGVHD will be based on IBMTR criteria[25]. Acute GVHD will be assessed at Day 100 at a consensus review. Recurrent aGVHD will be defined as the reappearance of aGVHD symptoms after day 100 whereas late acute GVHD will be defined as aGVHD occurring after day 100. Chronic GVHD will be diagnosed and graded according to consensus criteria[5]. Patients will be assessed for development of GVHD at 6 months and 12 months post-allograft. Assessments will evaluate the severity of symptoms and signs caused by GVHD and possible confounding factors. Additional assessments may be conducted if clinically indicated.

### 12.3.2 Secondary graft failure

Secondary graft failure is loss of ANC to < 500/μL for 14 consecutive days after initial recovery or loss of donor chimerism to < 10% donor after primary donor engraftment has been achieved not due to progressive malignancy within the marrow.

Patients with suspected graft failure will be evaluated with bone marrow biopsy to assess BM cellularity and assess for residual or recurrent disease, and molecular analyses of marrow.

### 12.3.3 Transplant related mortality (TRM)

TRM is defined as death at any time from the commencement of the study trial due to any cause other than disease relapse with the exception of automobile or other accidents. The incidence of TRM from the enrollment on protocol to 1 year after HSCT is a secondary end-point of the study.

### 12.3.4 Disease progression

Relapse of malignancy or progression of disease from the base-line documented pre-HSCT, is a secondary endpoint of this study and will be defined by an increasing number of malignant cells of recipient origin in the marrow over 5%, by the presence of circulating malignant cells, pathologic lymphadenopathy or by the presence of malignant cells at any other site. Radiologic studies, flow cytometric analysis or molecular studies of the marrow and/or peripheral blood, and/or biopsy of lymph nodes or other sites may also be obtained for the diagnosis of relapse or disease progression.

### 12.3.5 Immunologic recovery and immunization

Immune recovery will be performed at serial time points after transplant per standard of care as indicated in section 10. All time points will guide clinical decisions and be billable unless they are collected after a patient has completed immune recovery as marked by the initiation of vaccinations. Patients may be re-immunized from 12 months post-transplant according to the CDC guidelines. Percentage of patients who get vaccines on time and response to vaccination will be documented.

Patients who meet criteria for immunization (CD4 T cell > 200cells/μL, CD19 B cells > 50 cells/μL, IgG > 500 mg/dl, > 8 weeks after last dose of IVIG, > 6 months after last dose of Rituximab) will have pre-immunization titers measured and will be immunized according to institutional guidelines. Post-vaccine titers will be obtained to evaluate for vaccination response which is defined as at least a fourfold rise in specific antibody levels or a rise to a level considered protective per standard BMT practice.

### 12.3.6 Overall and progression-free survival

Overall survival is defined as the time of study enrolled to death from any cause; patients who remain alive will be censored at the time of last follow-up. Progression-free survival is defined as time from study enrollment to death or disease progression.

### 12.3.7 Percentage of patients who remain on immunosuppression

We will score patients as remaining on immunosuppression at 1 year if they remain on immunosuppressants at 1 year after the date of their stem cell infusion.

## 13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from study if any of the following events occurs:

- If at any time the patient is found to be ineligible for the protocol as designated in the section on *Criteria Subject Eligibility*, the patient will be removed from the study.
- If subject withdraws consent for continued participation. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care.
- Grade II-IV acute GVHD or chronic GVHD develops. If a patient is in the middle of a cycle, the patient may finish their cycle and then will be removed from study.
- Malignant disease relapse, progression, or death occurs.
- If a patient experiences severe unexpected adverse events, the treating physician or primary investigator can remove the patient from study at their discretion.

## 14.0 BIOSTATISTICS

This is a single arm phase 2 trial to investigate the efficacy of a weekly ixazomib regimen to reduce recurrent or late onset acute and chronic GVHD. The primary endpoint of this study is the incidence of recurrent or late acute grade II-IV aGVHD or chronic GVHD from the time of enrollment (day +100 to +150) to 1-year post-transplant time point. In addition to GVHD, the additional treatment failure criteria listed in 12.2 are considered as failures for the primary endpoint. Patients are evaluable for the primary endpoint if they complete at least one cycle of therapy. Patients who discontinue therapy prior to completing one cycle therapy for reasons unrelated to toxicity will be replaced. Patients who prematurely discontinue therapy after completing at least one cycle of therapy will remain evaluable for the primary endpoint.

The historical benchmark for this study is based on patients enrolled on MSK protocol 06-150. With these data, the estimated grade II-IV acute or chronic GVHD at 1-yr post-transplant among patients who could have been eligible to enroll on this study is 63% (no

patient died for reasons unrelated to GVHD). Therefore, the trial is designed such that a one-year incidence of recurrent or late acute grade II-IV GVHD or cGVHD of 40% would be considered promising for further development, whereas a 60% incidence would not be considered worthy of further study. Using these thresholds, we will utilize a Simon's two-stage optimal design based on the proportion of patients who develop GVHD. If more than 10 of the initial 18 patients have recurrent or late acute grade II to IV or cGVHD, the trial will terminate early due to lack of efficacy. Otherwise, the trial will continue to the maximum sample size of 46. If at the end of the study at least 23 out of 46 patients are free of recurrent or late acute grade II-IV GVHD or cGVHD the intervention will be considered promising for further development. The type I and type II errors are both set at 0.10.

In order to reduce patient risk, the study design includes early termination in the event of excessive graft failure or treatment-related mortality during the study period. Stopping rules for excessive failure and corresponding power calculations are given below. The calculations are based on marginal probabilities.

| Failure type | Number of failures needed to suspend the study | Failure rate in the population | Probability boundary is crossed |
|---|---|---|---|
| **Secondary graft failure** | 2 in the first 20 | 0.02 | 0.1 |
| | 3 at any point | 0.15 | 0.98 |
| **Transplant-related 1 yr. mortality** | 4 in the first 10 | 0.10 | 0.07 |
| | 5 in the first 20 | | |
| | 7 in the first 30 | | |
| | 8 in the first 40 | 0.30 | 0.96 |
| | 9 at any point | | |

In addition to the primary objective, there are a number of secondary and safety endpoints included in this study:

**Secondary endpoints:**

1. Cumulative incidence of cGVHD following study enrollment will be estimated. This will be calculated overall and by severity (moderate/severe). Disease progression and death in the absence of cGVHD are considered competing risks for this analysis.
2. The cumulative incidence of TRM from the time of study enrollment will be estimated, treating disease progression as a competing risk.
3. The cumulative incidence of disease progression from the time of study enrollment will be estimated, treating death in the absence of disease progression as a competing event.
4. The cumulative incidence of grade II-IV and III-IV acute GVHD will be estimated. Disease progression and death in the absence of acute GVHD are considered competing risks for this analysis.
5. Kaplan-Meier methods will estimate overall and progression-free survival from the time of study enrollment.
6. The proportion of patients who are able to discontinue all immunosuppressive medication at one year will be estimated along with a 95% confidence interval.
7. Graphical and summary measures will be used to describe CD3+CD4+ and CD3+CD8+ populations during the study window.

**Exploratory Endpoint:**

1. The proportion of patients who are able to get vaccines on time will be report with an exact 95% confidence interval. The vaccine response will be similarly described. Both timing and response will be estimated separately for each vaccine.

2. The treatment failure endpoint will be described separately for patients who enroll on study day +100 to day +125 and for patients who enroll on study day +125 to day +150.

**Safety Endpoint:**

1. The frequency and severity of adverse events will be tabulated.

## 15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

### 15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

### 15.3 Randomization

This research study does not require randomization procedures.

## 16.1 DATA MANAGEMENT ISSUES

Research Study Assistant (RSA) will be assigned to the study at MSKCC. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

### 16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

### 16.3 Data and Safety Monitoring

The Data and Safety Monitoring Plans (DSM) at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: Http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and the monitoring procedures will be established at the time of protocol activation.

## 17.1 PROTECTION OF HUMAN SUBJECTS

### 17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

### 17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent ***and*** is registered. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

An SAE must be reported to the IRB/PB within 5 calendar days of the event. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:.

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office. Potentially serious toxicities are an expected part of transplant therapy. Adverse events (AEs) and serious adverse events (SAEs) will be captured and reported as outlined in the Departmental Standard Working Procedure titled "Adult Bone Marrow Transplant (BMT) Adverse Event (AE) and Serious Adverse Event (SAE) Guide". In addition, the expected adverse events outlined in Table 11.2 will be captured.

**17.2.1**

AEs which are serious must be reported to Takeda Pharmaceuticals/ Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dost of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmaceuticals/ Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Takeda Pharmaceuticals/ Millennium Pharmacovigilance (or designee).

**17.3.2 Serious Adverse Event Definition**

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves

suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/$mm^3$ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

### 17.3.3 Procedures for Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should 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).

Since this is an investigator-initiated study, the principal investigator (Doris M. Ponce), also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Takeda Pharmaceuticals/ Millennium Pharmacovigilance (or designee):

**Fatal and Life Threatening SAEs** within 24 hours but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event.

**All other serious (non-fatal/non life threatening) events** within 5 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Takeda Pharmaceuticals/ Millennium Pharmacovigilance.

The sponsor-investigator must fax or email the de-identified SAE Form per the timelines above. A sample of an SAE Form will be provided.
The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Takeda Pharmaceuticals/ Millennium.
Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at the institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Takeda Pharmaceuticals/ Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s).

**SAE and Pregnancy Reporting Contact Information**

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

### 17.3.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Takeda Pharmaceuticals/ Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.
If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmaceuticals/ Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Takeda Pharmaceuticals/ Millennium)

### 17.3.5 Administrative Requirements

17.2.5.1 Products complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Pharmaceuticals/ Millennium Quality representative.

**For Product Complaints,**

call MedComm Solutions at

877-674-3784 (877 MPI DRUG)

(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmaceuticals/ Millennium Pharmacovigilance (refer to Section 17.2.3).

## 18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

## 19.0 REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-1826.
2. Devine SM, Carter S, Soiffer RJ, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: results of the blood and marrow transplant clinical trials network protocol 0303. *Biol Blood Marrow Transplant*. 2011;17(9):1343-1351.
3. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2003;9(4):215-233.
4. Pavletic SZ, Carter SL, Kernan NA, et al. Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation. *Blood*. 2005;106(9):3308-3313.
5. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-4016.
MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant*. 2002;8(7):387-394.
7. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012;158(1):30-45.
8. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496.
9. Soiffer RJ, Lerademacher J, Ho V, et al. Impact of immune modulation with anti-T-cell antibodies on the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies. *Blood*. 2011;117(25):6963-6970.
10. Mielcarek M, Storer BE, Boeckh M, et al. Initial therapy of acute graft-versus-host disease with low-dose prednisone does not compromise patient outcomes. *Blood*. 2009;113(13):2888-2894.
11. Deeg HJ. How I treat refractory acute GVHD. *Blood*. 2007;109(10):4119-4126.
12. Couriel D, Caldera H, Champlin R, Komanduri K. Acute graft-versus-host disease: pathophysiology, clinical manifestations, and management. *Cancer*. 2004;101(9):1936-1946.
13. Westin JR, Saliba RM, De Lima M, et al. Steroid-Refractory Acute GVHD: Predictors and Outcomes. *Adv Hematol*. 2011;2011:601953.

14. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood*. 2003;102(2):756-762.
15. Ceberio I, Devlin SM, Sauter C, et al. Sirolimus, tacrolimus and low-dose methotrexate based GVHD prophylaxis after non-ablative or reduced intensity conditioning in related and unrelated donor allo-HCT. *Leuk Lymphoma*. 2014:1-31.
16. Sauter CS, Barker JN, Lechner L, et al. A phase II study of a nonmyeloablative allogeneic stem cell transplant with peritransplant rituximab in patients with B cell lymphoid malignancies: favorably durable event-free survival in chemosensitive patients. *Biol Blood Marrow Transplant*. 2014;20(3):354-360.
17. Nencioni A, Schwarzenberg K, Brauer KM, et al. Proteasome inhibitor bortezomib modulates TLR4-induced dendritic cell activation. *Blood*. 2006;108(2):551-558.
18. Blanco B, Perez-Simon JA, Sanchez-Abarca LI, et al. Bortezomib induces selective depletion of alloreactive T lymphocytes and decreases the production of Th1 cytokines. *Blood*. 2006;107(9):3575-3583.
19. Koreth J, Stevenson KE, Kim HT, et al. Bortezomib-based graft-versus-host disease prophylaxis in HLA-mismatched unrelated donor transplantation. *J Clin Oncol*. 2012;30(26):3202-3208.
20. Pai CC, Chen M, Mirsoian A, et al. Treatment of chronic graft-versus-host disease with bortezomib. *Blood*. 2014;124(10):1677-1688.
21. Gupta N, Liu G, Berg D, Kalebic T, Gomez-Navarro J. Clinical pharmacokinetics of intravenous and oral MLN9708, an investigational proteasome inhibitor: an analysis of data from four phase 1 monotherapy studies. *Journal of the American Society of Hematology (ASH Annual Meeting)*. 2010;116(21):757-758.
22. Gupta N, Saleh M, Venkatakrishnan K. Flat-dosing versus BSA-based dosing for MLN9708, an investigational proteasome inhibitor: population pharmacokinetic (PK) analysis of pooled data from 4 phase-1 studies *Journal of the American Society of Hematology (ASH Annual Meeting)*. 2011;118(21):622-623.
23. Gupta N, Venkatakrishnan K, Noe D, et al. A drug-drug interaction study between the strong CYP3A4 inhibitor ketoconazole (keto) and ixazomib citrate (MLN9708), an investigational, orally active proteasome inhibitor, in patients with advanced solid tumors or lymphoma. *J Clin Oncol (ASCO Annual Meeting)*. 2013;31:Abstract 2555.
24. Assouline S, Chang J, Rifkin R, et al. MLN9708, a novel investigational proteosome inhibitor, in patients with relapsed/refractory lymphoma: results of a phase 1 dose-escalation study. *Journal of the American Society of Hematology (ASH Annual Meeting)*. 2011;118(21):1148.
25. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *British Journal of Haematology*. 1997;97(4):855-864.

## 20.0 APPENDICES

N/A