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CLINICAL TRIALS NETWORK

# Multicenter Phase II, Double-blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Multiple Myeloma

**BMT CTN PROTOCOL 1302**
**VERSION 3.0**


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## PROTOCOL SYNOPSIS – BMT CTN 1302 PROTOCOL

### Multicenter Phase II, Double-blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Multiple Myeloma

**Co-Principal Investigators**: Qaiser Bashir, Parameswaran Hari, Taiga Nishihori

**Study Design:** The study is designed as a Phase II, multi-center double-blind trial that randomizes patients with high risk MM to ixazomib maintenance or placebo 60-120 days after allogeneic hematopoietic transplantation (HCT).

**Primary Objective:** The primary objective of this randomized trial is to compare progression free survival from randomization as a time to event endpoint between patients randomized to ixazomib maintenance or placebo.

**Secondary Objectives:** Secondary objectives are to describe for each treatment arm: rates of grade II-IV and III-IV acute GVHD, chronic GVHD, best disease response rates, disease progression, transplant related mortality, overall survival, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, incidence of infections, and health-related quality of life.

**Eligibility Criteria:** Patients aged ≥ 18.0 years and ≤ 70.0 years at the time of enrollment, with:

1) high risk multiple myeloma in partial response (PR) or better with no prior progression *and* are ≤ 24.0 months from autologous HCT (single or planned tandem), or are ≤ 24.0 months from initiation of systemic anti-myeloma therapy with no autologous HCT; *or*
2) high risk multiple myeloma in very good partial response (VGPR) or better with 1 prior progression which occurred ≤ 24.0 months after autologous HCT (single or planned tandem), or ≤ 24.0 months after initiation of systemic anti-myeloma therapy with no autologous HCT; *or*
3) standard risk multiple myeloma in VGPR or better with 1 prior progression which occurred ≤ 24.0 months from autologous HCT (single or planned tandem); *or*
4) plasma cell leukemia in VGPR or better with no prior progression *and* are ≤ 18.0 months after autologous HCT, or are

≤ 18.0 months after initiation of systemic anti-myeloma therapy with no autologous HCT

Patients must have a HLA-matched related or unrelated donor willing to donate peripheral blood progenitor cells and meet one of the following criteria:

a. A sibling donor who is a 6/6 match at HLA–A and –B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*

b. A related donor (other than sibling) who is a 8/8 match for HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR*

c. An unrelated donor who is an 8/8 match at HLA–A, –B, –C, and –DRB1 (at high resolution using DNA-based typing)

**Treatment Description:** All patients will undergo conditioning regimen with fludarabine (120 mg/m$^2$), melphalan (140 mg/m$^2$) and bortezomib (1.3 mg/m$^2$ ) combination. GVHD prophylaxis will use the combination of tacrolimus and methotrexate. Randomization to ixazomib maintenance or placebo will occur at the time of maintenance therapy initiation (between Days 60 and 120 post-transplant). Maintenance with ixazomib will consist of 12 x 28-day cycles at a dose of 3 mg on Days 1, 8 and 15, with adjustments depending on toxicity. Ixazomib will continue for a maximum of 12 cycles (28 days/cycle). Patients randomized to placebo will follow the same treatment and dose schedule as those randomized to ixazomib maintenance.

**Accrual:** The sample size for this study is 110 randomized patients with a target enrollment of 138 patients to achieve that sample size.

**Accrual Period:** The estimated accrual period is 3 years

**Study Duration:** Patients will be followed for 2 years post transplant for all endpoints. In addition, patients will be followed only for second primary malignancies until all patients have completed 2 years of follow up.

**Interim Analysis:** There will be no formal interim analysis for futility or efficacy for this trial.

**Stopping Guidelines:** The key safety endpoints to be monitored are the rate of TRM at Day 100 post-transplant in all transplanted subjects, Grade III-IV acute GVHD at Day 100 post-transplant, and Grade III-IV acute GVHD rates at Day 60 post-randomization within treatment arm. Monitoring of the key safety endpoints will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will

be notified in order that the DSMB can be advised. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures (MOP).

# STUDY SCHEMA

**Aim:** To determine the impact of maintenance and allogeneic transplant in high risk multiple myeloma

| **Inclusion Criteria** | **Exclusion Criteria** |
|---|---|
| 1. Age ≥ 18.0 and ≤ 70.0 years at the time of enrollment<br>2. Patient must meet ONE of the disease criteria outlined in table 1 below.<br>3. Patients must have a HLA-matched related or unrelated peripheral blood stem cell donor that meet one of the following criteria: A sibling donor who is a 6/6 match at HLA–A and–B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR* a related donor (other than sibling) who is a 8/8 match for HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) *OR* an unrelated donor who is an 8/8 match at HLA–A, –B, –C, and –DRB1 (at high resolution using DNA-based typing).<br>4. Cardiac function: Ejection fraction > 40%<br>5. Estimated creatinine clearance greater than 40 mL/minute<br>6. Pulmonary function: DLCO ≥ 40% (adjusted for hemoglobin) and FEV1 ≥ 50%<br>7. Liver function: total bilirubin < 2x the upper limit of normal and ALT/AST < 2.5x the upper normal limit<br>8. Effective methods of birth control as described in the protocol<br>9. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care. | 1. Karnofsky Performance Score < 70%<br>2. Prior allogeneic HCT<br>3. Non secretory multiple myeloma (defined as normal serum and urine immunofixation and normal serum free light chain assay).<br>4. Uncontrolled bacterial, viral or fungal infections (undergoing appropriate treatment and with progression of clinical symptoms).<br>5. Seropositive for the human immunodeficiency virus (HIV).<br>6. Active Hepatitis B or C determined by serology and/or NAAT.<br>7. Hypersensitivity to bortezomib, boron or mannitol.<br>8. Grade 2 or higher sensory peripheral neuropathy.<br>9. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.<br>10. Pre-planned pre-emptive or prophylactic administration of donor lymphocytes.<br>11. CNS involvement with MM (CSF positivity for plasma cells or a parenchymal CNS plasmacytoma<br>12. Presence of fluid collection that interferes with methotrexate clearance.<br>13. Known GI disease or GI procedure that could interfere with the oral absorption of MLN9708 (ixazomib).<br>14. Prior cancers except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years, which is in remission, will be reviewed on a case-by-case basis by the Protocol Officer or one of the Protocol Chairs<br>15. Multi-organ involvement by amyloidosis or evidence of amyloidosis-related organ dysfunction.<br>16. Received radiation therapy within ≤ 3.0 weeks before transplant |

## Table 1: Disease Criteria for Eligible Patients

| Disease | Disease Status | Prior Progression | Prior Therapy/Auto HCT |
|---|---|---|---|
| High Risk[1] Multiple Myeloma | **≥ PR** | **None** | ≤ 24.0 months after autologous HCT (single or planned tandem), or after initiation of systemic anti-myeloma therapy with no autologous HCT |
| High Risk[1] Multiple Myeloma | **≥ VGPR[2]** | **1** | progression or relapse ≤ 24.0 months after autologous HCT (single or planned tandem), or after initiation of systemic anti-myeloma therapy with no autologous HCT |
| Standard Risk Multiple Myeloma | **≥ VGPR[2]** | **1** | progression or relapse ≤ 24.0 months after single or planned tandem autologous HCT |
| Plasma Cell Leukemia | **≥ VGPR** | **None** | ≤ 18.0 months after autologous HCT, or after initiation of systemic anti-myeloma therapy |

***Immune Suppression Taper*:**
Patients without GVHD
Tacrolimus
- Taper to initiate at least Day 90 and completely off at Day 180.

**Primary endpoint:**
- Progression free survival as a time to event endpoint from randomization

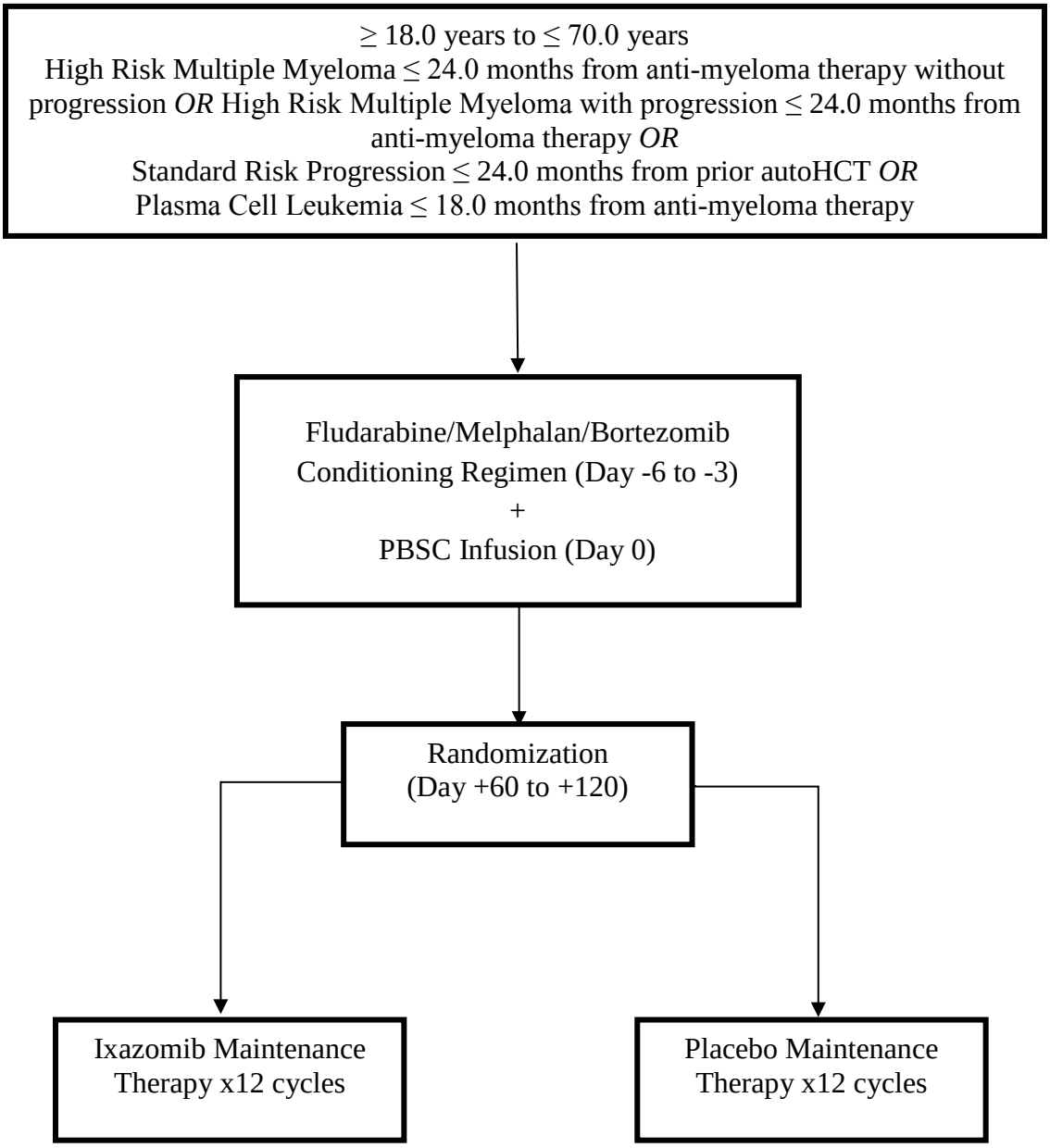
**Secondary endpoints:**
- Grades II-IV and III-IV acute GVHD
- Chronic GVHD
- Best response
- Disease progression
- Treatment-related mortality
- Toxicity
- Rates of infections
- Overall survival
- Rate of non-randomization
- Health-Related Quality of Life

[1]High Risk is defined as one or more of the following detected at any time prior to enrollment: del13 by conv. karyotyping only; hypodiploidy, 1q amplification or 1p deletion, t(4;14), t(14;16), t(14;20) or deletion of 17p by FISH or conv. karyotyping; or high risk criteria based on GEP.

[2]Patients with one prior progression without measurable monoclonal paraprotein at the time of disease progression or relapse (< 1.0 g/dl in serum or < 200 mg/24 hrs in urine) may be considered to have met VGPR criteria if < 5% plasma cells in bone marrow *and* ≥ 90% decline in the difference between involved and uninvolved FLC levels from baseline (time of progression/relapse).

Patients with IgG kappa multiple myeloma receiving daratumumab: International Myeloma Working Group criteria for VGPR may not be achieved since daratumumab is known to increase the IgG kappa spike. In such cases the FLC and marrow may be used to establish VGPR, as above, with prior approval from the protocol co-chairs.

# OUTLINE OF TREATMENT PLAN



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# CHAPTER 1

# 1. BACKGROUND AND RATIONALE

## 1.1. Multiple Myeloma and Risk Stratification

Chromosomal abnormalities can be detected in up to 90% of patients with multiple myeloma (MM).[1] Several chromosomal abnormalities detected by conventional karyotyping or fluorescence *in situ* hybridization (FISH) have significant implications on patient outcomes. Among those associated with poor outcomes and considered to be high risk disease by the International Myeloma Consensus Recommendations include, chromosomal 13 or 13q deletion, t(4;14) and del(17p) by conventional cytogenetics, and t(4;14), t(14;16), and del(17p) detected by FISH.[2] High-risk MM remains incurable and autologous hematopoietic cell transplantation (HCT) only results in transient disease control at best in part due to intrinsic and/or acquired drug resistance.[3-5] Several large scale studies have helped characterize the high risk chromosomal abnormality in MM and the results are summarized in Table 1.1.

**TABLE 1.1: SIGNIFICANCE OF CHROMOSOMAL CHANGES ON SURVIVAL IN MYELOMA PATIENTS**

| Study | N | Therapeutic modalities | Chromosomal abnormality (Cytogenetics and/or FISH) | Outcomes |
|---|---|---|---|---|
| IFM991 (IFM99-02[6]/IFM99-03[7]/IFM99-04[8]) | 1064 | • IFM99-02: auto HCT, thalidomide maintenance vs. placebo<br>• IFM99-03: auto HCT, followed by sibling donor RIC allogeneic HCT<br>• IFM99-04: tandem auto HCT with anti-IL6 antibody (vs. none) | • del(13): 48%<br>• t(11;14): 21%<br>• t(4;14): 14%<br>• hyperdiploidy: 39%<br>• *MYC* translocations: 13%<br>• del(17p): 11% | • Univariate analysis: del(13), t(4;14), nonhyperdiploidy, and del(17p) negatively impacted EFS and OS.<br>• Multivariate analysis: t(4;14) and del(17p) were prognostic for EFS and OS. |
| ECOG9486/ ECOG9487[9] | 351 | Conventional chemotherapy | • del(13): 54.2%<br>t(4;14): 12.7%<br>• t(14;16): 4.6%<br>• t(11;14): 15.8%<br>• del(17p): 10.7% | • Univariate analysis: t(4;14)(p16.3;q32), t(14;16)(q32;q32), del(17p13.1), and del(13) had inferior OS.<br>t(4;14)(p16.3;q32), t(14;16)(q32;q32) and del(13) had worse PFS.<br>del(17p13.1) was of marginal significance for PFS. |
| Spanish GEM-2000[10] | 260 | 6 cycles of VBCMP/VBAD followed by auto HCT | • t(11;14): 13%<br>• t(4;14): 11%<br>• t(14;16): 3%<br>• *P53* deletion: 8.5% | • t(4;14), *RB* or *P53* deletions had shorter survival.<br>• *RB* deletions without other abnormality had similar outcomes (as no FISH abnormality)<br>• Multivariate analysis: t(4;14) and *RB* deletion with other abnormalities (age > 60, higher S-phase cells, or advanced stage) retained their independent prognostic significance |
| Canadian Expanded Access Program[11] | 130 | Rev/Dex for relapsed/refractory MM | • del(13q): 41.5%<br>• t(4;14): 21.5%<br>• del(17p13): 9.2% | • del(13q) or del(17p13) resulted in a lower response rate.<br>• del(17p13) with shorter survivals (OS 4.7 months) |

**Abbreviations:** auto, autologous; del, deletion; ECOG, Eastern Cooperative Oncology Group; EFS, event free survival; FISH, fluorescence in situ hybridization; HCT, hematopoietic cell transplantation; IFM, Intergroupe Francophone du Mye´lome; IL, interleukin; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; RB, retinoblastoma; Rev/Dex, lenalidomide (Revlimid) and dexamethasone; RIC, reduced intensity conditioning; VBCMP/VBAD, vincristine, BCNU, cyclophosphamide, melphalan, prednisone/vincristine, BCNU, adriamycin, and dexamethasone

Multiple studies have shown inferior survivals in MM patients harboring high risk chromosomal abnormalities including del(13) by cytogenetics, and t(4;14), t(14;16) and del(17) by FISH.[1,9-11] MM patients with retinoblastoma (*RB*) deletions (chromosome 13) without other abnormalities by FISH have similar outcomes with MM patients without chromosomal abnormalities (46 vs. 54 months, $P = .3$),[10] however, detection of del(13) by conventional cytogenetics remains a marker of poor prognosis.[12] Deletion of 17p13 carries extremely poor prognosis and is associated with a shorter overall survival (OS), more aggressive disease, extramedullary involvement (including CNS) and hypercalcemia.[13-16] In a report of 105 MM patients treated with high-dose melphalan followed by autologous HCT, patients with *TP53* deletions had a lower median progression-free survival (PFS) of 11.8 months vs. 25 months for those without deletions (p=0.08), and OS was 14.6 months vs. 45.9 months, respectively.[14]

Chromosome 1 abnormalities also portend poor prognosis.[17-19] The group from Mayo Clinic reported that translocations involving chromosome 1p were associated with an elevated plasma cell labeling index ($P = .004$)[17]. In univariate analysis, structural abnormalities of chromosome 1 showed inferior 5-year OS (18.3% for 1p deletions and 23.1% for 1p translocations). Frequency of chromosome band 1q21 amplification (Amp1q21) was investigated by the University of Arkansas group.[20] Amp1q21 was seen in 43% of newly diagnosed MM and 72% of relapsed MM. Newly diagnosed MM patients with Amp1q21 had inferior 5-year event free survival (EFS) and OS after tandem transplant (under Total Therapy 2 protocol) at 38% and 62%, respectively. Multivariate analysis demonstrated Amp1q21 being an independent poor prognostic factor.[20] The group developed a 70-gene model using a gene expression profiling (GEP) on purified plasma cells.[18] Thirty percent of the 70 high risk genes mapped to chromosome 1 ($P < .001$). The ratio of mean expression levels of up-regulated to down-regulated genes defined a high risk score which was present in 13% of MM patients with shorter durations of complete response (CR), EFS, and OS.[18] The high risk score was also an independent predictor of outcomes in multivariate analysis ($P < .001$).

Based on abovementioned studies, high risk MM can be considered as those with any of the following chromosomal changes detected by FISH: t(4;14), t(14;16), del (17p), and abnormalities of chromosome 1 (1q21 amplifications; 1p deletion); deletion 13 or hypodiploidy by cytogenetics.

## 1.2. Impact of Novel Agents in High risk Multiple Myeloma

Recent data suggest that bortezomib based regimens may be effective in overcoming poor risk cytogenetic features which may in part be due to a central role of NF-κB pathway in MM pathogenesis and the activity of bortezomib through the pathway.[21] Several studies evaluating the impact of novel agents on treatment outcomes in high risk MM are summarized in Table 1.2.

## TABLE 1.2: INFLUENCE OF BORTEZOMIB ON MYELOMA OUTCOMES ON SELECTED STUDIES

| Study | N | High risk features | Treatment | Outcomes |
|---|---|---|---|---|
| PETHEMA[22] | 60 (newly diagnosed, HCT ineligible) | • Rb deletion by FISH (n=13) vs. no deletion (n=20)<br>• IgH translocations by FISH (n=8) vs. no IgH (n=20) | VMP | • RR: 100% vs. 66% for Rb deletion vs. no (*P* = .16)<br>• RR: 88% vs. 82% for Rb deletion vs. no (*P* = .7)<br>• PFS and EFS were similar in patients with Rb deletion or IgH translocation |
| SUMMIT investigators[23] | 202 (relapsed/ refractory) | Chromosome 13 deletion (15%) | bortezomib ± dexamethasone | Multivariate analysis: Increased CRP (*P* = .011) and abnormal cytogenetics (*P* = .01) were associated with shortened TTP, but not chromosome 13 deletion |
| Total Therapy 3[24] | 303 (newly diagnosed) | • 70 gene-defined GEP high risk | Total therapy 3 (bortezomib containing, including tandem autologous HCT) | • GEP-defined *FGFR3* subgroup had superior CR duration, EFS, and OS compared to TT2 (no bortezomib)<br>• Shorter EFS and OS for t(4;14) in TT2 was not seen in TT3 |
| VISTA trial[25] | 682 (newly diagnosed, HCT ineligible) | • t(4;14), t(14;16), or 17p deletion (n=26 vs n=142 with standard cytogenetic profiles) | VMP | • Same rate of CR (28%), similar TTP (*P* = .55), and OS (*P* = .99) with standard cytogenetic profiles.<br>• Results similar with inclusion of 13q deletion patients (n=75). |
| IFM[26] | 507 (newly diagnosed, < 65 yrs, HCT eligible) | • t(4;14): n=106<br>• del(17p): n=54<br>• (compared to VAD treated population) | Bortezomib + dexamethasone x 4 cycles (before autologous HCT) | • Improved EFS and OS with bortezomib in t(4;14) patients: 4-year OS 63% vs. 32%; *P* < .001<br>• No difference for EFS (*P* = .32) and OS (*P* = .49) in del(17p) patients |
| GMMG-HD3/ GMMG-HD4[27] | 315 (newly diagnosed, HCT eligible) | • t(4;14): 13%<br>• del(17p13):10%<br>• +1q21: 36% | • Induction: VAD x3 or related regimens (n=244), TAD (n=29), or PAD (n=42)<br>• Maintenance: a-IFN (n=118), thalidomide (n=66), bortezomib (n=37), or none (n=94) | • 3-year PFS with del(13q14), +1q21, and del(17p13) were 27% (vs. 46%; *P* = .013), 24% (vs. 50%; *P* = .018), and 50% (vs. 81%; *P* = .018).<br>• On multivariate analysis, t(4;14) and del(17p13) significantly impacted PFS and OS |
| HOVON-65/GMMG-HD4[28] | 354 (Newly diagnosed, HCT eligible) | • t(4;14): 14.2%<br>• del(17p13): 10.6%<br>• +1q21: 32.3% | • Arm A: VAD, autologous HCT, thalidomide maintenance<br>• Arm B: PAD, autologous HCT, bortezomib maintenance | • del(17p13) was independent predictor for PFS (*P* < .001) and OS (*P* < .001) in arm A, however, no significant effect on PFS (*P* = .28) and OS (*P* = .12) was seen in arm B.<br>• Median PFS 26.2 months (arm B) vs. 12 months (arm A) in del(17p13); *P* = .024<br>• 3-year OS 69% (arm B) vs. 17% (arm A) in del (17p13); *P* =.028 |

**Abbreviations:** CR, complete response; CRP, C-reactive protein; EFS, event free survival; FGFR3, fibroblast growth factor receptor 3; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; HCT, hematopoietic cell transplantation; IFM, Intergroupe Francophone du Mye´lome; IgH, immunoglobulin heavy chain; PAD, bortezomib, Adriamycin, and dexamethasone; PFS, progression-free survival; Rb, retinoblastoma; RR, response rate; SUMMIT, Study of Uncontrolled Myeloma Managed with Proteasome Inhibition Therapy; TAD, thalidomide, adriamycin, and dexamethasone; TT, Total Therapy; TTP, time to progression; VAD, vincristine, adriamycin, and dexamethasone; VMP, bortezomib (Velcade), melphalan, and prednisone

Taken together, the addition of novel agents, like bortezomib, may overcome known adverse prognostic features such as t(4;14).[24,25,27,29] However, conflicting results of bortezomib regarding the survival advantage for MM patients with del(17p) have been reported.[27,29,30] Outcomes of MM patients with high risk chromosomal abnormality remain poor and there is a significant unmet need for the development of effective therapy.

## 1.3. Current Status of Allogeneic Hematopoietic Cell Transplantation for Multiple Myeloma

Allogeneic HCT remains the only potentially curative option for MM; however, the exact place of this modality in the treatment algorithm of MM is controversial. Recent reports from two large US centers where majority of MM patients had relapsed or refractory disease at the time of allogeneic HCT showed long-term OS being generally between 20% and 40%.[31,32]In a report by the European Group for Blood and Marrow Transplantation (EBMT), 229 MM patients received an allograft with reduced intensity conditioning (RIC), and transplant-related mortality (TRM) at 1-year was 22%. The 3-year OS and PFS were 41% and 21%, respectively.[33] The adverse PFS was associated with chemoresistant disease (relative risk (RR) of 2.9), suggesting no benefit with progressive disease. Chronic GVHD was associated with better OS and PFS underscoring the importance of a graft-versus-myeloma effect.[33] Overall, the results of allogeneic HCT have continued to improve significantly over the years as was seen in a steady decline in TRM by the Center for International Blood and Marrow Transplant Research (CIBMTR) analysis.[34] However the relapse after allogeneic HCT remains a challenge,[34] and the emerging data suggest that the outcomes of allogeneic HCT could be further improved with the use of novel agents.[35]

## 1.4. Autologous HCT Followed by Allogeneic HCT with Nonmyeloablative Conditioning

The encouraging results of RIC allogeneic HCT renewed the interest in further optimizing this treatment modality. A strategy of autologous HCT followed by RIC allogeneic HCT was introduced. In an early report by the Seattle group, 52 patients received a single fraction of 2-Gy total body irradiation (TBI) and allogeneic HCT from human leukocyte antigen (HLA)-identical siblings with mycophenolate mofetil (MMF) and cyclosporin (CSA) GVHD prophylaxis after initial autologous HCT. The CR rate was 57% with an overall response rate (ORR) of 83%. The OS was 78% with a median follow-up of 552 days.[36] In a similar approach, 17 patients with MM, after autografting with high dose melphalan, received a RIC regimen consisting of fludarabine (180 mg/m$^2$), melphalan (100 mg/m$^2$), and anti-thymocyte globulin (ATG: 30 mg/kg) followed by an allografting from related (n=7), mismatched related (n=2), or unrelated (n=8) donors. Day +100 TRM was 11% and CR rate increased from 18% after autologous HCT to 73% after allogeneic HCT.[37] Long-term outcomes of 102 MM patients from Seattle where allogeneic HCT from HLA matched siblings were performed with 2-Gy TBI, with or without fludarabine (30 mg/m$^2$ on Days -4 through -2) following auto HCT.[38]

The 5-year non-relapse mortality (NRM) was 18% with a CR-rate of 65%. The 5-year OS and PFS were 64% and 36%, respectively.[38] Only limited cytogenetic data were available and cytogenetic abnormalities did not impact TRM, PFS, or OS. Using a similar approach, the Italian group treated 100 newly diagnosed MM patients in a prospective multicenter trial where patients received VAD induction, followed by high dose melphalan and autologous HCT, then allografting from HLA-matched sibling donors with 2-Gy TBI conditioning.[39] GVHD prophylaxis was MMF and CSA. The CR was 53%. Cumulative incidence of grade II-IV acute GVHD was 38% with 50% rate of extensive chronic GVHD. TRM was 11.4%. The median EFS was 3.1 years and the median OS was not reached after a median follow-up of 5 years. Several randomized trials have compared tandem autologous HCT with autologous followed by RIC allogeneic HCT approach and the results are summarized in Table 1.4.1.[40- 47]

# TABLE 1.4.1: RANDOMIZED CLINICAL TRIALS COMPARING TANDEM AUTOLOGOUS HCT WITH AUTOLOGOUS HCT FOLLOWED BY RIC ALLOGENEIC HCT

| Study | Era/ Patients/ Donor | N/Age | Induction | Conditioning/ GVHD prophylaxis | TRM/GVHD | Response |
|---|---|---|---|---|---|---|
| **Garban et al[7] (IFM99-03/99-04)** | • 2000-2004<br>• DSS I-III, del13 by FISH, β2MG > 3mg/L<br>• MRD | • N=284<br>• IFM99-03=65 (46 completed therapy)<br>• IFM99-04=219 (166 completed therapy)<br>• Age <65 | • VAD x 3-4<br>• Collection<br>• MEL200 | • IFM99-03: If MRD available, Bu (2mg/kg/d PO x 2 days) + Flu (25 mg/m$^2$/d x 5 days) + ATG (2.5 mg/kg/d x 5 days)<br>• GVHD: CSA+MTX<br>• IFM 99-04: If no MRD available, randomized to (A) 2$^{nd}$ auto HCT, Dex (40mg x 4 days) + MEL220 or (B) 2$^{nd}$ auto HCT MEL220 + Dex + B-E8 (250 mg total dose) | • IFM99-03: TRM 10.9%<br>• Grade II-IV aGVHD=23.9 %<br>• cGVHD: extensive 35.7% | • IFM99-03:<br>• ≥ VGPR: 37.8% at 1 mo after auto HCT and 62.2% at 2 mo after allo HCT<br>• IFM99-04: ≥ VGPR was 34% after 1$^{st}$ auto HCT and 51% after 2$^{nd}$ auto HCT |
| **Bruno et al.[40]** | • 1998-2004<br>• DSS II or III | • N=162<br>• 80 had MRD, 58 completed allo HCT<br>• 82 had no MRD, 46 completed<br>• Age ≤ 65 | • VAD x 2-3<br>• Cy 3-4 g/m$^2$ ± paclitaxel 250 mg → G-CSF mobilization | • If MRD + →MEL200 → allo HCT TBI 200cGy<br>• GVHD: CSA+MMF<br>• If no MRD; refused allo HCT; or ineligible donor → double auto MEL100 or MEL140-200 | • TRM similar (*P* = .09) after median f/u 45 mo<br>• Grade II-IV aGVHD 43%; extensive cGVHD 32% at 2-yr* | • Allo vs Auto<br>• CR rate: 55% (auto-allo) vs. 26% (tandem auto: *P* = .004) |
| **Rosiñol et al.[43] (PETHEMA/GEM-2000)** | • 1999-2004 | • 280 eligible but only 110 received 2$^{nd}$ HCT<br>• Age < 70 yr | • VBMCP/VBAD x 6 → 1$^{st}$ auto HCT, if < nCR, then 2$^{nd}$ auto HCT (CVB or MEL200) or allo.<br>• If MRD and < 65 → allo (n=25), or 2$^{nd}$ auto HCT(n=85) | • MEL200 + auto HCT<br>• RIC allo HCT: Flu 25 mg/m$^2$ x 5 days + MEL70 x 2 days<br>• GVHD: CSA+MTX | • TRM 16% (allo) vs. 5% (auto: *P* = .09)<br>• Grade II-IV aGVHD 32%<br>• cGVHD 66% | • CR rate: 40% (allo) vs. 11% (auto: *P* = .001) |
| **Krishnan et al.[45] (BMT CTN 0102)** | • 2003-2007<br>• Standard-risk disease defined as: β2MG<4 mg/L & no del 13 by cytogenetics<br>• No progression after initial chemo | • N=710<br>• tandem auto (SR n=436; HR n=48)<br>• auto-allo (SR n= 111; HR n=37)<br>• Age <70 yr | • At least 3 cycles of chemo<br>• MEL200 | • If MRD available: auto-allo (TBI 200cGy)<br>• GVHD: CSA+MMF<br>• If No MRD: tandem auto<br>• MEL200 → randomized to observation vs. thalidomide 200mg/d + Dex 40/d x 4 consecutive days/month x 1-yr | • TRM: 4% (auto) vs 11% (allo: *P* < .0001)<br>• Grade II-IV aGVHD at 100-d 26%<br>• cGVHD at 2-yr 54% | • CR-rate: 45% (auto) vs. 58% (allo: *P* = .007) |
| **Björkstrand et al.[48,49] (EBMT/NMAM 2000)** | • 2001-2005<br>• ≥ SD on 1$^{st}$ line therapy.<br>• FISH del13q14 n=214;<br>• del13 in 92; (tandem auto HCT, n=63; auto-allo HCT, n=29) | • N=357<br>• If MRD, then auto-allo (n=91)<br>• If no donor, then tandem auto HCT (n=249)<br>• Age < 70 yr | • VAD or similar (no novel agents) | • MEL200 →<br>• Allo = Flu 30 mg/m$^2$/d x 3 days + TBI 2Gy (n=91)<br>• GVHD: CSA+MMF<br>• 2$^{nd}$ auto MEL200 (n=104)<br>• or no treatment (n=145) | • NRM at 60 mo: 18% (allo) vs. 3% (auto: *P* < .001)<br>• aGVHD: grade II 9%, grade III 8%, grade IV 2%<br>• extensive cGVHD 23% | • CR-rate within 60 mo: 56% (allo) vs. 44% (auto: *P* .007) |
| **Lokhorst et al.[46] (HOVON-50/54)** | • 2003-<br>• DSS II-III | • N=260<br>• (donor = 122; no donor = 138)<br>• Age:18-65 yr | • HOVON-50<br>• VAD or TAD<br>• Stem cell harvest with CAD (Cy+Adria+Dex) | • MEL 200 → maintenance with IFN or thalidomide (50 mg/d)<br>• N=3 received 2$^{nd}$ auto HCT<br>• If had MRD → HOVON-54 (allo)<br>• TBI 2Gy | • NRM: 16% (donor) vs. 3% (No donor: *P* < .001)<br>• aGVHD=48%<br>• Grade III=4%<br>• Grade IV=5% | • CR rate: 43% (donor) vs. 37% (no donor: *P* = .67) |

| Study | Era/ Patients/ Donor | N/Age | Induction | Conditioning/ GVHD prophylaxis | TRM/GVHD | Response |
|---|---|---|---|---|---|---|
| | | | | • GVHD: CSA+MMF | • extensive cGVHD 55% | |
| **Knop et al[47] (German DSMM V)** | • 10/2002 – 03/2007<br>• High risk patients (del 13 by FISH; newly diagnosed; DSS II-III)<br>• MRD & MUD | • N=199<br>• (allo performed in 126 – 76 MUDs)<br>• (2nd auto HCT in 73)<br>• Age ≤ 60 (median age 53) | • Anthracycline/Dex based induction x 4 → MEL auto HCT | • After 1st auto HCT randomized to 2nd auto HCT with MEL or allo-HCT<br>• Allo: Flu 30 mg/m$^2$ x 3 days) + MEL140<br>• (ATG for MUDs) | • TRM at 2-yr 12.7% (allo) | • CR rate: 59% (allo) vs. 32% (tandem auto: *P* = .003) |

**Abbreviations:** aGVHD, acute GVHD: allo, allogeneic; ATG, anti-thymocyte globulin; auto, autologoush; B-E8, anti-IL-6 antibody; bu, busulfan; □2MG, beta-2 microglobulin; cGVHD, chronic GVHD; CI, cumulative incidence; CR, complete response; CSA, cyclosporin; CVB, cyclophosphamide, etoposide, and BCNU; Cy, cyclophosphamide; del13, deletion 13; Dex, dexamethasone; DSS, Durie-Salmon staging; FISH, fluorescence in situ hybridization; flu, fludarabine; G-CSF, granulocyte-colony stimulating factor; GVHD, graft-versus-host-disease; HR, high risk; IFM, Intergroupe Francophone du Mye´lome; MEL200, high dose melphalan at 200 mg/m$^2$; MMF, mycophenolate mofetil; MRD, matched related donor; MTX, methotrexate; NRM, non-relapse mortality; SR, standard risk; TAD, thalidomide, adriamycin, and dexamethasone; TBI, total body irradiation; TRM, transplant-related mortality; VAD, vincristine, adriamycin (doxorubicin), dexamethasone; VBCMP/VBAD, vincristine, BCNU, cyclophosphamide, melphalan, prednisone/vincristine, BCNU, adriamycin, and dexamethasone; VGPR, very good partial response; yr, year
*No association between aGVHD, or cGVHD and response.

Giaccone et al.[41] Unchanged results after longer follow up of 7-years. The RR to salvage therapies was significantly higher and OS from relapse was significantly longer after the allograft then the 2nd autograft (*P* = 0.01).

As summarized in Table 1.4.2, two randomized trials have shown superiority of autologous followed by RIC allogeneic HCT approach leading to better PFS and OS,[40,48,49] and one randomized trial demonstrated superior PFS.[43] The other trials including the largest trial performed in the US by the BMT CTN (BMT CTN 0102, Krishnan and Pasquini et al.) showed that while allogeneic HCT is associated with superior CR rate, the PFS and OS are similar to tandem autologous HCT approach. The TRM is generally higher with allogeneic HCT and it is conceivable that, with recent reductions seen in early TRM, the outcomes with allogeneic HCT may improve, particularly in patients with high risk disease in whom the outcomes remain dismal regardless of the therapy used[45].

## TABLE 1.4.2: COMPARISON OF OUTCOMES BETWEEN TANDEM AUTOLOGOUS HCT AND AUTOLOGOUS FOLLOWED BY RIC ALLOGENEIC HCT IN PROSPECTIVE RANDOMIZED TRIALS

| Study | Transplant type | TRM | CR rate | EFS/PFS | OS | Relapse rate |
|---|---|---|---|---|---|---|
| Garban et al[7] | tandem auto HCT | 5% | | 35 m | 47.2 m (*P* = .07) | |
| | auto/allo HCT | 10.9% at 100-day | | 31.7 m | 35 m | |
| Bruno et al[40] | tandem auto HCT | 2% (CI at 2-yr) | 26% | 29 m | 54 m | |
| | auto/allo HCT | 10% (CI at 2-yr) | 55% (*P* = .004) | 35 m (*P* = .02) | 80 m (*P* = .01) | |
| Knop et al[47] | tandem auto HCT | - | 32% | | 72% (*P* = .22) | |
| | auto/allo HCT | 12.7% | 59% (*P* = .003) | | 60% | |
| Rosiñol et al[43] | tandem auto HCT | 5% | 11% | 31 m | 58 m | |
| | auto/allo HCT | 16% (*P* = .07) | 40% (*P* = .001) | not reached (*P* = .08) | not reached (*P* = .9) | |
| Krishnan and Pasquini et al[45] | tandem auto HCT | 4% (CI at 3-yr) | 45% | 46% (*P* = .671) | 80% (*P* =.191) | |
| | auto/allo HCT | 11% (CI at 3-yr) | 58% (*P* = .007) | 43% | 77% | |

| Study | Transplant type | TRM | CR rate | EFS/PFS | OS | Relapse rate |
|---|---|---|---|---|---|---|
| Björkstrand et al[48,49] | tandem auto HCT | 3% (CI at 3-yr) | 41% at 60m | 12% at 96 m | 36% at 96 m | 82% (*P* = .0002) |
| | auto/allo HCT | 13% (CI at 3-yr; *P* = .0004) | 50% at 60m | 22% at 96 m (*P* = .027) | 49% at 96 m (*P* = .03) | 60% |
| Lokhorst et al[46]** | tandem auto HCT & maintenance post 1st auto HCT | 3% | | 22% at 6 ys | 55% at 6 yr | 77% |
| | auto/allo HCT | 16% (*P* < .001) | | 28% at 6 yr | 55% at 6 yr | 55% |

**Abbreviations:** allo, allogeneic; auto, autologous; CI, cumulative incidence; CR, complete response; EFS, event-free survival; HCT, hematopoietic cell transplantation; m, month(s); OS, overall survival; PFS, progression-free survival; TRM, treatment-related mortality; yr, year
*Trend towards increased OS with tandem autologous HCT
**PFS longer for patients who actually received allogeneic HCT

## 1.5. Impact of Chromosomal Abnormalities on Outcomes after allogeneic HCT

There is an unmet need for better therapeutic approaches for MM patients with high risk chromosomal abnormalities. Allogeneic HCT may have a role for such patients; however, the prospective transplant trials have fully addressed this question due to a limited number of patients. There are limited data from retrospective studies suggesting benefits of allogeneic HCT in patients with high risk chromosomal abnormalities such as t(4;14). In a German study of 101 MM patients treated with allogeneic HCT with fludarabine/melphalan ± ATG conditioning, the impact of genetic abnormality detected by FISH was evaluated.[50] Patients with del(17p13) achieved less CR (7% vs. 56%; *P* = .001). Univariate analysis demonstrated a higher relapse rate in patients with del(13q14) (*P* = .006) and del(17p13) (*P* = .003). In multivariate analyses, only del(13q14) (hazard ratio (HR): 2.34; *P* = .03) and del(17p13) (HR: 2.24; *P* = .0.04) significantly influenced the incidence of relapse, whereas for EFS, only age (HR 2.8; *P* = .01) and del(17p13) (HR: 2.05; *P* = .03) retained their negative prognostic value. No difference was seen for t(4;14), suggesting that it might be overcome by allogeneic HCT.[50] In a retrospective multicenter French registry study of 143 MM patients transplanted between 1999 and 2008, impact high risk cytogenetics was analyzed.[51] Nineteen received myeloablative conditioning regimens while RIC regimens were used in 77%, with inclusion of ATG in 48%. Patients with t(4;14), del(17p), or t(14;16) were grouped as poor risk group. There were no significant differences between the two groups (standard vs. high) for 3-year PFS, OS and progression rate. The data indicated that allogeneic HCT could potentially benefit high risk MM population.[51] In a single center retrospective analysis by El-Cheikh et al., the feasibility of matched unrelated donor (MUD) allogeneic HCT for MM patients was highlighted.[52] Forty-three high risk MM including relapsed disease (n=30), newly diagnosed with high risk cytogenetic (del13q, del17, or t(4;14), or less than PR after autologous HCT, were treated with RIC allogeneic HCT (MUD, n=17; MRD, n=23). Conditioning regimens were fludarabine-busulfan-ATG (n=33) or fludarabine-TBI 2Gy (n=7). At 2 years, OS and PFS were 59% and 42% for MUD, and 66% and 44% for MRD, respectively (P = .241).[52] In the updated EBMT NMAM-2000 study, superior outcomes of patients with chromosome 13 deletion by cytogenetics were reported after autologous HCT followed by RIC allogeneic HCT. The PFS and OS were 21% and 47% vs 5% (*P* = .026), and 31% (*P* = .154) with autologous followed by RIC allogeneic HCT and tandem autologous HCT, respectively.[49] The observation suggests that RIC allogeneic HCT might overcome poor prognostic impact of del(13).[49] In summary, the chromosomal abnormality is important in defining high risk MM, however, emergent data suggest that allogeneic HCT may at least partly be able to overcome the poor risk conferred by these genetic changes. Prospective clinical trials with novel transplant approaches are needed to better define the role of allogeneic HCT in high risk MM patients.

## 1.6. Bortezomib

Bortezomib for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), bortezomib in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high dose chemotherapy with bone marrow transplant. Bortezomib is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

### 1.6.1. Scientific Background

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.[53] In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation.[54-66] Notably, bortezomib induces apoptosis in cells that over-express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[67]

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets, including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-$\alpha$, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor $\kappa$B (NF-$\kappa$B) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[68-75]

### 1.6.2. Clinical Experience

To date, more than 436,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m$^2$/dose, with

DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[76] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m$^2$/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m$^2$/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m$^2$/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.[77-80]

The safety and efficacy of bortezomib in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse)[81] and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy).[82] In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous treatments received bortezomib, 1.3 mg/m$^2$ on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade[83] were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039)[84], also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m$^2$ IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 treatment cycles as induction therapy, followed by 1.3-mg/m$^2$ bortezomib weekly on Days 1, 8, 15, and 22 of a 5-week cycle for 3 cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to 4 treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with bortezomib versus 18% with dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus < 1% with dexamethasone ($p < 0.0001$). The CR + nCR (near CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow-up, overall survival was significantly longer ($p =$

0.0013) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the bortezomib arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (p = 0.0005). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (p = 0.0098). Updated response rates and survival data were reported for M34101-039.[85] The updated CR + PR rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, p = 0.0272). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm (p = 0.0002).

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study.[86] The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study[87] was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of bortezomib, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant.[88] The study was designed to determine the benefit of adding bortezomib to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were randomized to receive nine 6-week cycles of melphalan 9mg/m$^2$ and prednisone 60 mg/m$^2$ on Days 1 to 4, alone or in combination with bortezomib 1.3 mg/m$^2$ by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the bortezomib (VMP) group compared to 34% in the MP group (p = 0.001). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group (p

= 0.000001) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

The VISTA study update after extended follow-up of 25.9 months,[89] confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% (p = 0.0032). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive bortezomib.

Based on investigator-reported best responses to subsequent therapies, patients relapsing after therapy with a novel agent were not intrinsically more resistant than after receiving a traditional agent.

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months).[90] In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for VMP was 56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85)[91.]

## 1.7. Use of Bortezomib during and after Allogeneic HCT

Recent studies have shown that the outcomes of MM patients undergoing autologous HCT can be significantly improved with the post HCT maintenance therapy.[92-95] On the other hand, there is only limited information available regarding maintenance therapy following allogeneic HCT. Several pre-clinical and clinical studies have suggested that bortezomib can be safely used following allogeneic HCT, without exacerbation of GVHD and with good clinical responses. In addition, the data suggest that administration of bortezomib with allogeneic HCT may decrease the risk of GVHD while preserving graft-versus tumor (GVT) effect.

### 1.7.1. Pre-clinical Data

Bortezomib has been shown to promote apoptosis of alloreactive T cells during GVHD in murine models via reduction of 20S proteasome function and diminished NF-κB activity.[96] In murine models of HLA-mismatched allogeneic HCT, early administration of bortezomib protects against acute GVHD without impairing engraftment with preservation of GVT responses.[97,98] However, delayed administration of bortezomib (5-7 days after BMT) resulted in significant acceleration of GVHD-dependent morbidity with significant increases of type 1 tumor necrosis factor α (TNF-α) receptor transcription in gastrointestinal cells and with significant increases of TNF-α, interleukin

1β, and IL-6 levels in the serum.[97] In another study, it was demonstrated that $CD4^+$ T cells are the primary source of TNF-α during the early phases of GVHD and bortezomib-induced GVHD-dependent mortality was preventable by depletion of $CD4^+$ T cells from the donor graft.[99] In addition, bortezomib may exert immunomodulatory activity by modulating toll-like receptor induced activation of dendritic cells.[100] Bortezomib may selectively deplete alloreactive T cells where NF-κB expression is increased.[101] Other group has also shown that NF-κB is a critical regulator of alloresponsiveness and bortezomib is effective in preventing early post transplant GVHD lethality in murine models.[102]

### 1.7.2. Clinical Data on Bortezomib after Allogeneic HCT

The efficacy of bortezomib for MM patients relapsing after allogeneic HCT has been reported.[103,104] Bruno et al. reported an overall response rate of 61% and CR rate of 22% with bortezomib ± steroids in MM patients who relapsed after allogeneic HCT.[105] In a report from European centers, donor-lymphocyte infusion (DLI) was given to MM patients with relapsed (n=48) and persistent (n=15) disease following nonmyeloablative allogeneic HCT.[106] The median OS after DLI was 23.6 months which was probably long due to the fact that 83.3% of patients not responding or relapsing after DLI were sensitive to additional treatment with thalidomide and bortezomib.[106] Kröger et al. reported the use of bortezomib on 18 MM patients without progressive disease after RIC allogeneic HCT (the median time: 268 days) to enhance or maintain remission status.[107] Severe neuropathy (grade III/IV) was only observed in patients treated concomitantly with cyclosporine (3 vs. 0; $P = .06$). The number of circulating $CD3^+$ cells declined significantly ($P = .03$). There was only a mild aggravation of existing acute or chronic GVHD of the skin with bortezomib (3/18).[107] In another report, 37 patients with progressive (n=32) or residual (n=5) MM after RIC allogeneic HCT received bortezomib with (n=26) or without (n=11) dexamethasone.[108] Overall response rate was 73% (n=27; 7 CR; 7 VGPR; 13 PR) and only 2 patients experienced reactivation or worsening of GVHD symptoms. Thirty two MM patients who achieved on PR after allogeneic HCT were treated with DLI.[109] If no CR was achieved, the patients were treated with thalidomide, lenalidomide, or bortezomib. Overall, 27% patients converted to CR after DLI, which was increased to 59% with addition of novel agents. There was no correlation between achievement of CR and incidence of acute and chronic GVHD.

The use of bortezomib after allogeneic HCT is deemed efficacious to control MM and does not appear to exacerbate GVHD.

### 1.7.3. Combining Bortezomib with Allogeneic HCT

Several groups combined bortezomib to high dose melphalan for MM and showed promising results.[110,111,112] Bortezomib has been combined with RIC conditioning regimen of fludarabine and melphalan. Twenty two MM patients with multiple myeloma in first VGPR or CR received allogeneic HCT at Moffitt Cancer Center.[113] Conditioning consisted of fludarabine, melphalan and bortezomib given at 1.3 mg/m2 on Day -3 (n=13) and fludarabine and melphalan (n=9). Stringent CR was achieved in 68% of patients at their best responses after allogeneic HCT. The 2-year PFS and OS were 74.8% and 77.5%, respectively. NRM at 6 months was non-relapse mortality of 10.5%.[113] The regimen of fludarabine, melphalan and bortezomib was deemed feasible. Overall,

these data provide evidence that use of bortezomib in peri-transplant period is effective and is associated with reasonable response rates and possibly a protective effect on GVHD.

Currently, there is no consensus on maintenance therapy following allogeneic HCT.[114, 115] Among other novel agents, lenalidomide has also been used after allogeneic HCT in 30 MM patients in the HOVON76 trial.[115] However, lenalidomide maintenance was poorly tolerated and patients also had rapid onset of GVHD. Further studies are thus needed to demonstrate the safety of efficacy of lenalidomide maintenance after allogeneic HCT.

#### 1.7.4. Bortezomib for GVHD Prophylaxis

Bortezomib has been tested for GVHD prevention with encouraging results. Early administration of bortezomib after mismatched allogeneic HCT protects against acute GVHD without adversely effecting engraftment. In a phase II/II clinical trial, 45 patients with hematological malignancies undergoing 1 or 2 antigen or allele HLA-mismatched allogeneic HCT received GVHD prophylaxis with tacrolimus + low dose methotrexate + bortezomib at 1 of 3 dose levels.[116,117] Conditioning regimen consisted of fludarabine (30 mg/m$^2$ IV) and busulfan (0.8 mg/kg) on Days -5 through -2. Bortezomib dose levels were 1, 1.3, and 1.5 mg/m$^2$ IV on Days +1, +4, and + 7. The dose level 1.3 mg/m$^2$ was identified as the maximum tolerated dose. The 180-day cumulative incidence of grade II-IV acute GVHD was 22% and 1-year cumulative incidence of chronic GVHD was 29%. The 2-year cumulative incidence of NRM and relapse were 11% and 38%, respectively.

#### 1.7.5. Modified Conditioning Regimen

Patients who were enrolled prior to Version 2.0 of the protocol received post-transplant bortezomib on Days -2, +1, +4, and +7. Following the transplant of 15 patients on study, the protocol-specified conditioning regimen was modified due to the incidence of unanticipated toxicities among patients early post-transplant. Beginning with protocol Version 2.0, patients will receive the modified conditioning regimen described in Table 2.4.3, which reduces the bortezomib to one dose pre-transplant, and early post-transplant toxicity will be monitored closely.

### 1.8. Ixazomib (MLN9708)

#### 1.8.1. Preclinical Experience

Please refer to the current MLN9708 Investigator's Brochure (IB).

#### 1.8.2. Clinical Experience

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies., sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available in both intravenous and oral formulations. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia,

systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 IB.

### 1.8.3. Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (Tmax) of approximately 0.5 to 2.0 hours and terminal t1/2 after multiple dosing of approximately 5 to 7 days118. 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 BSA119. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. Please refer to the current IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 5% of dose). In vitro studies of liver microsomes show that MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 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 MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, 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. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

### 1.8.4. Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with

different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1.8.1.

**Table 1.8.1 Ongoing Studies of Oral MLN9708**

| **Trial/ Population** | **Description** | **Doses Investigated** |
|---|---|---|
| C16003<br>RRMM<br>N = 58 | PO, twice weekly (TW), single agent | 0.24-2.23 mg/m$^2$, TW<br>MTD: 2 mg/m$^2$<br>DLT: rash, thrombocytopenia |
| C16004<br>RRMM<br>N = 52 | PO, weekly (W), single agent | 0.24-3.95 mg/m$^2$, W<br>MTD: 2.97 mg/m$^2$<br>DLT: rash, nausea, vomiting, diarrhea |
| C16005<br>NDMM<br>N = 65 | PO, W, combination with LenDex<br>28 day cycle | 1.68-3.95 mg/m$^2$, W<br>MTD: 2.97 mg/m$^2$<br>DLT: nausea, vomiting, diarrhea, syncope<br>RP2D*: 4 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m$^2$) |
| C16006<br>NDMM<br>N = 28 | PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone | Arm A*: 3-3.7 mg, fixed dose, TW<br>DLT: rash, thrombocytopenia, subileus<br>Arm B*: 5.5 mg, fixed dose, W<br>DLT: Esophageal ulcer |
| C16007<br>RR-AL<br>N = 6 | PO, W, single agent | 4-5.5 mg, fixed dose*, W<br>MTD: 4 mg<br>DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest |
| C16008<br>NDMM<br>N=11 | PO, TW, combination with LenDex 21 day cycle | 3-3.7 mg fixed dose* W<br>MTD: 4 mg<br>DLT: |
| C16009<br>Solid tumors, Lymphomas<br>N = 22 | PO, W, single agent | 5.5 mg fixed dose* W |
| C16010<br>RRMM<br>N = 1 | PO, W, combination with LenDex | 4 mg fixed dose* W |
| TB-MC010034<br>RRMM<br>N = 5 | PO, W, single agent in 1s part of study then in combination with LenDex in 2$^{nd}$ part | 3 mg fixed dose* W<br>DLT: thrombocytopenia, nausea, hypertension, diarrhea |

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m$^2$ BSA dosing; 4 mg ~ equivalent to 2.23 mg/m$^2$ BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m$^2$ BSA dosing.

### 1.8.5. Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies (C16003, C16004, C16007, and C16009) is shown in Table 1.8.2.

**Table 1.8.2 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (TEAE) (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)**

| Primary System Organ Class | Preferred Term and Incidence N=146 n (%) |
|---|---|
| **Subjects with at Least One Adverse Event 135 (92)** | |
| Gastrointestinal disorders 102 (70) | Nausea 68 (47); Diarrhea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14) |
| General disorders and administration site conditions 98 (67) | Fatigue 71 (49); Pyrexia 31 (21); Edema peripheral 15 (10) |
| Blood and lymphatic system disorders 77 (53) | Thrombocytopenia 60 (41); Anemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10) |
| Nervous system disorders 63 (43) | Headache 20 (14); Dizziness 18 (12) |
| Metabolism and nutrition disorders 60 (41) | Decreased appetite 39 (27) Dehydration 21 (14) |
| Respiratory, thoracic and mediastinal disorders 60 (41) | Cough 22 (15); Dyspnea 21 (14) |
| Skin and subcutaneous tissue disorders 60 (41) | Rash macular 17 (12) |
| Musculoskeletal and connective tissue disorders 56 (38) | Arthralgia 20 (14); Back pain 17 (12) |
| Infections and infestations 54 (37) | Upper respiratory tract infection 21 (14) |

Source: MLN9708 Investigator's Brochure Edition 7

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

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

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1.8.3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

**Table 1.8.3 Summary of Most Common (At Least 10% of Total) TEAE (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)**

| Primary System Organ Class | Preferred Term and Incidence<br>N= 96<br>n (%) |
|---|---|
| Subjects with at Least One Adverse Event 135 (92) | |
| Gastrointestinal disorders 70 (73) | Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhea 22 (23) |
| General disorders and administration site conditions 64 (67) | Fatigue 37 (39); Edema peripheral 20 (21); Pyrexia 19 (20) |
| Skin and subcutaneous tissue disorders 57 (59) | Rash 13 (14) |
| Nervous system disorders 46 (48) | Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11) |
| Musculoskeletal and connective tissue disorders 45 (47) | Back pain 18 (19); Muscle spasms 10 (10) |
| Blood and lymphatic system disorders 42 (44) | Thrombocytopenia 28 (29); Anemia 22 (23); Neutropenia 19 (20) |
| Infections and infestations 40 (42) | Upper respiratory tract infection 17 (18); |
| Metabolism and nutrition disorders 38 (40) | Decreased appetite 11 (11) |
| Respiratory, thoracic and mediastinal disorders 34 (35) | Dyspnea 13 (14); Cough 11 (11) |
| Psychiatric disorders 23 (24) | Insomnia 15 (16) |

Source: MLN9708 Investigator's Brochure Edition 7.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

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

The clinical experience with MLN9708 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 MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors[120], non-Hodgkin's disease, Hodgkin's disease[121], relapsed and/or refractory multiple myeloma[122,123], relapsed or refractory systemic light chain amyloidosis[124], and newly diagnosed multiple myeloma [125,126,127] to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

### 1.8.6. Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];
2. Carfilzomib expansion cohort
3. Proteasome Inhibitor-Naïve expansion cohort.
4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated[128,129].

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1- 11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1.8.4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

| **Table 1.8.4 Study C16004, Oral Mln9708, Single Agent, Given Weekly: Most Common TEAE as of 30 April 12 (N= 52)** | |
|---|---|
| Most Common (> 20%) Any Grade and Irrespective of Cause | Thrombocytopenia (54%)<br>Fatigue (48%)<br>Nausea (44%), diarrhea (44%)<br>Vomiting (37%)<br>Decreased appetite (33%)<br>Rash* (31%)<br>Anemia (25%)<br>Neutropenia (23%) |
| Drug-Related Grade ≥ 3 in > 5% of patients | Thrombocytopenia (38%)<br>Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6% |

Source: MLN9708 Investigator's Brochure Edition 7

* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and not related Grade 4 elevation in creatinine(1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly, Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4 mg. Following the establishment of the MTD,

patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed[130].

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38% and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1.8.5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

**Table 1.8.5 Study C16007, Oral MLN9708, Single Agent Given Weekly, Most Common TEAE as of 30 April 12 (N = 14)**

| | |
|---|---|
| Most Common (> 20%)<br>Any Grade and Irrespective of Cause | Nausea (50%)<br>Fatigue (36%)<br>Thrombocytopenia (29%)<br>Diarrhea (29%)<br>Decreased Appetite (21%)<br>Peripheral Edema (21%)<br>Dyspnea (21%)<br>Abdominal pain (21%) |
| Drug-Related Grade ≥ 3 in more than 3 Patients | Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients |

Source: MLN9708 Investigator's Brochure Edition 7

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and standard medical interventions,

which may include dose reductions and supportive care. Please refer to the MLN9708 IB for further information.

1.8.7. Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 $mg/m^2$ given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 $mg/m^2$ compromised the maximal dosing of lenalidomide and that the dose of 2.23 $mg/m^2$ is very tolerable and clinically active, Millennium designated 2.23 $mg/m^2$ as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 $mg/m^2$ has been translated into a fixed dose of 4mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral edema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1.8.6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

**Table 1.8.6 Study C16005: Oral MLN9708 Given Weekly In Combination With Lenalidomide And Dexamethasone, Most Common TEAE as of 30 April 2012**

| | |
|---|---|
| Most Common (> 20%) Any Grade and Irrespective of Cause | Fatigue (37%)<br>Nausea (34%)<br>Constipation (31%)<br>Vomiting (28%)<br>Diarrhea (26%)<br>Thrombocytopenia (23%)<br>Upper respiratory tract infection (22%)<br>Anemia and edema peripheral ( 20% each) |
| Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients | Nausea, vomiting (n=3 each)<br>Thrombocytopenia, lymphopenia, rash pruritic (n=2 each ) |

Source: MLN9708 Investigator's Brochure Edition 7.

[a] Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localized infection, gastrointestinal hemorrhage, respiratory syncytial virus (RSV) pneumonia fecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral edma, asthenia, hyponatremia vomiting, diarrhea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia. One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

## 1.9. Rationale for the Study

The treatment outcomes of high risk multiple myeloma patients remain suboptimal even in the era of novel agents and abundance of available regimens. There is considerable unmet need to improve their therapeutic outlook and the role of allogeneic HCT in this population remains to be defined. The introduction of reduced intensity regimen has resulted in reduced TRM in allogeneic HCT for patients with myeloma. Emerging single center experience supports the feasibility of reduced intensity conditioning regimen of fludarabine, melphalan plus bortezomib in patients with multiple myeloma[111]. However, myeloma relapse still need to be reduced in order to maximize the efficiency of this therapeutic approach in high risk patients. This clinical trial addresses these two challenges with allogeneic HCT. First, the addition of bortezomib to the conditioning regimen can optimize the anti-myeloma effect of melphalan against malignant plasma cells. Second, the addition of a novel maintenance drug may further reduce the risk of disease relapse long enough in order for the graft versus myeloma to take effect.

Given the small number of myeloma patients treated with an allogeneic transplant at individual institutions, we propose to perform a multicenter study evaluating the conditioning regimen of fludarabine, melphalan plus bortezomib followed by allogeneic HCT from a HLA-matched related or unrelated donor in patients with high risk multiple myeloma. Patients will be randomized to

placebo-controlled maintenance therapy of ixazomib (MLN9708) after allografting and the maintenance therapy will be prescribed for one year. The study will assess the novel conditioning regimen in high risk population as well as the efficacy of ixazomib in preventing disease relapse/progression following allogeneic HCT. The results of this trial will assist in understanding the role of this novel agent in post allogeneic HCT maintenance and will assist in designing a definitive trial for this population with high risk multiple myeloma.

# CHAPTER 2

# 2. STUDY DESIGN

## 2.1. Study Overview

This is a multicenter, phase II, double-blind placebo controlled prospective trial, which randomizes patients with high risk multiple myeloma to maintenance ixazomib or matching placebo 60-120 days after allogeneic HCT with Peripheral Blood Stem Cells (PBSC). Patients will undergo a conditioning regimen with a fludarabine, melphalan and bortezomib combination followed by HLA-matched related or unrelated donor allografting. GVHD prophylaxis will be the combination of tacrolimus and methotrexate.

The starting doses of ixazomib and placebo are 3 mg, administered orally once a day on Days 1, 8, and 15 of a 28-day cycle. After 3 cycles of maintenance therapy at 3 mg, ixazomib and placebo dose will be increased to 4 mg if the drug is tolerated. Dose escalation and de-escalation on BOTH treatment arms may be performed depending on tolerability or development of adverse reactions. No dose re-escalation is permitted following a dose reduction. The planned dose of oral ixazomib and placebo ranges from 2.3 mg per day to 4 mg per day on Days 1, 8, and 15 of a 28-day cycle for 12 cycles maximum. To maintain the blind in patients receiving placebo, the number/dose of placebo capsules administered will be identical to the number/dose of ixazomib capsules the patient would receive if randomized to ixazomib.

## 2.2. Hypothesis and Objectives

### 2.2.1. Hypothesis

Ixazomib maintenance therapy results in improved progression-free survival in patients with high risk multiple myeloma after allogeneic HCT.

### 2.2.2. Primary Objectives

To compare progression-free survival as a time to event endpoint from the time of randomization between patients randomized to ixazomib versus placebo maintenance in patients with high risk multiple myeloma.

### 2.2.3. Secondary Objectives

Below are the secondary objectives for each arm of maintenance therapy, when applicable.

1. Estimate cumulative incidence of grades II-IV and III-IV acute GVHD.
2. Estimate cumulative incidence of chronic GVHD.
3. Estimate best disease response rates.
4. Estimate cumulative incidence of disease progression rates.
5. Estimate overall survival rates.

6. Estimate cumulative incidence of treatment related mortality rates.
7. Estimate the incidence of grade ≥ 3 adverse events.
8. Estimate the incidence of infections.
9. Describe health-related quality of life
10. Additionally, we will estimate the proportion of patients who are willing and able to be randomized to maintenance and describe the frequencies of events that preclude randomization.
11. Estimates for the primary and key secondary endpoints for each arm of maintenance therapy will be described post transplant.

## 2.3. Patient Eligibility

Patients must meet specified eligibility criteria to be registered on the study.

### 2.3.1. Inclusion Criteria

1. Age ≥ 18.0 years and ≤ 70.0 years at the time of enrollment.
2. Patients must meet ONE of the criteria outlined in either a, b, c, OR d:
    a. Patients with high risk multiple myeloma in partial response (PR) or better with no prior progression *and* are ≤ 24.0 months after autologous HCT (single or planned tandem), or are ≤ 24.0 months after initiation of systemic anti-myeloma therapy for patients without prior autologous HCT; *or*
        i. High risk is defined by the presence of any one of the following detected at any time prior to enrollment: deletion of chromosome 13 by conventional cytogenetics, hypodiploidy, abnormality in chromosome 1(1q amplification or 1p deletion), t(4;14), t(14;16), t(14;20) or deletion of 17p by fluorescence in situ hybridization (FISH) or conventional karyotyping; high risk criteria based on commercially available gene expression profiling (GEP)[1]
    b. Patients with high risk multiple myeloma (see criterion 2.a.i. above) in very good partial response (VGPR) or better with 1 prior progression which occurred ≤ 24.0 months after autologous HCT (single or planned tandem), or ≤ 24.0 months after initiation of systemic anti-myeloma therapy for patients without prior autologous HCT; *or*
        i. Patients with one prior progression without measurable monoclonal paraprotein at the time of disease progression or relapse (< 1.0 g/dl in serum or < 200 mg/24hrs in urine) may be considered to have met VGPR criteria if < 5% plasma cells in bone marrow *and* ≥ 90% decrease

[1] Patients with high risk multiple myeloma based on GEP alone require approval by the BMT CTN 1302 Study Chairs prior to enrollment.

in the difference between involved and uninvolved FLC levels from baseline (time of progression/relapse).

ii. In patients with IgG kappa MM receiving daratumumab: International Myeloma Working Group criteria for VGPR may not be achieved since daratumumab is known to increase the IgG kappa spike. In such cases the FLC and marrow may be used to establish VGPR, as above, with prior approval from the protocol co-chairs.

c. Patients with standard risk multiple myeloma in VGPR or better (see criteria 2.b.i. and 2.b.ii. above) at the time of enrollment with 1 prior progression ≤ 24.0 months from single or planned tandem autologous HCT; *or*

d. Patients with primary plasma cell leukemia in VGPR or better with no prior disease progression *and* are ≤ 18.0 months after autologous HCT, or are ≤ 18.0 months after initiation of anti-myeloma therapy without prior autologous HCT.

3. Patients must have a related or unrelated donor willing and able to donate peripheral blood stem cells that meets one of the following criteria:

   a. A sibling donor who is a 6/6 match at HLA–A and –B (intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) and must be willing to donate peripheral blood stem cells and meet institutional criteria for donation *OR*

   a. A related donor (other than sibling) who is a 8/8 match for HLA–A, –B, –C (at intermediate or higher resolution) and –DRB1 (at high resolution using DNA-based typing) and must be willing to donate peripheral blood stem cells and meet institutional criteria for donation *OR*

   b. An unrelated donor who is an 8/8 match at HLA–A, –B, –C, and –DRB1 (at high resolution using DNA-based typing) and must be willing to donate peripheral blood stem cells and meet institutional criteria for donation.

4. Cardiac function: Ejection fraction > 40%

5. Estimated or calculated creatinine clearance greater than 40 mL/minute (using the Cockcroft-Gault formula and actual body weight)

6. Pulmonary function: DLCO ≥ 40% (adjusted for hemoglobin) and FEV1 ≥ 50%

7. Liver function: total bilirubin < 2x the upper limit of normal and ALT/AST < 2.5x the upper normal limit (patients with Gilbert's Disease are permitted to exceed the defined bilirubin value of 2x the upper limit of normal, however measurements of direct bilirubin should be done to confirm this diagnosis).

8. Female subjects (unless postmenopausal for at least 1 year before the screening visit, or surgically sterilized), agree to practice two (2) effective methods of contraception at the same time, or agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)

through 90 days after the last dose of maintenance therapy (see Section 2.6.2 for definition of postmenopausal).

9. Male subjects (even if surgically sterilized) must agree to one of the following: practice effective barrier contraception (see Section 2.6.4.1 for list of barrier methods), or practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of from the time of signing the informed consent through 90 days after last dose of maintenance therapy.
10. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
11. Able to comply with the study visit schedule and other protocol requirements.

2.3.2. Exclusion Criteria

1. Karnofsky Performance Score < 70%
2. Prior allogeneic HCT
3. Patient with purely non-secretory multiple myeloma [absence of monoclonal protein (M protein) in serum as measured by electrophoresis and immunofixation and the absence of Bence Jones protein in the urine defined by the use of conventional electrophoresis and immunofixation techniques and the absence of involved serum free light chain > 100 mg/L].
4. Planned pre-emptive/prophylactic administration of donor lymphocytes (as per section 2.5.2)
5. Central Nervous System (CNS) involvement with multiple myeloma defined as CSF positivity for plasma cells or a parenchymal CNS plasmacytoma
6. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment.
7. Presence of fluid collection (ascites, pleural, or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated.
8. Patients seropositive for the human immunodeficiency virus (HIV).
9. Patient with active Hepatitis B or C determined by serology and/or NAAT.
10. Patients with hypersensitivity to bortezomib, boron or mannitol.
11. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 (ixazomib) including difficulty swallowing.
12. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
13. Patients with ≥ grade 2 sensory peripheral neuropathy.

14. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
15. Female patients who are lactating or pregnant
16. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years, which is in remission, will be reviewed on a case-by-case basis by the Protocol Officer or one of the Protocol Chairs.
17. Patients with multi-organ involvement by amyloidosis or evidence of amyloidosis related organ dysfunction.
18. Failure to have fully recovered (i.e., no toxicities > Grade 1 by CTCAE version 4.0) from the reversible effects of prior chemotherapy.
19. Patient with serious medical of psychiatric illness likely to interfere with participation on this clinical study
20. Participation in clinical trials with other investigational agents not included in this trial, ≤ 14.0 days of enrollment on this trial and throughout its duration.
21. Patients who have received radiation therapy within 3 weeks before transplant. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy.
22. Patients unable or unwilling to adhere to the study assessment schedule.

2.3.3. Donor Exclusion Criteria

1. Donors will be excluded if they are an identical twin of the recipient.
2. Females who are pregnant (positive serum β HCG) or uninterruptible breastfeeding will be excluded.
3. HIV seropositive donors will be excluded.
4. Donors receiving experimental therapy or investigational agents will be excluded unless approved by the protocol chairs and protocol officer.
5. Donors not willing and able to donate PBSC will be excluded

Related and unrelated donors will be identified according to institutional guidelines.

2.3.4. Patient Eligibility Criteria to Begin Maintenance Therapy

In order to be eligible for randomization, patients must have sufficiently recovered from their allogeneic transplant. Between Day +60 and Day +120 after allogeneic HCT, patients will be

randomized to receive either ixazomib maintenance or placebo. If patients do not meet the eligibility criteria for initiating maintenance, they will continue to be followed per the protocol.

Eligibility criteria for initiating maintenance are as follows:

1. Platelet count ≥ 75,000/mm$^3$
2. Absolute neutrophil count (ANC) ≥ 1,000/mm$^3$.
3. Total bilirubin < 2x the upper limit of the normal range (ULN), except in patients with Gilbert's syndrome.
4. ALT/AST < 2.5x the upper normal limit
5. No ≥ grade 2 visceral (gut or liver) acute GVHD. No ≥ Grade 3 any other acute GVHD.
6. Patient should not have disease progression of myeloma (according to Section 3.1.3)
7. Peripheral Neuropathy ≤ Grade 3 or Grade 2 with pain by CTCAE version 4.0 criteria
8. Patients must be tolerating GVHD prophylaxis.
9. Females of childbearing potential (FCBP)[2] must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 14.0 days of initiating maintenance

2.3.5. Patient Exclusion Criteria to Begin Maintenance Therapy

1. Female patients who are lactating
2. Presence of non-hematologic toxicities that have not resolved to ≤ Grade 1 by CTCAE version 4.0
3. Patients who have received radiotherapy ≤ 14.0 days before initiating maintenance. Use of radiation therapy ≤ 14.0 days before administration of maintenance study drug in the absence of disease progression may be permitted with written study chair and/or protocol officer approval.
4. Central nervous system involvement with multiple myeloma defined as CSF positivity for plasma cells or a parenchymal CNS plasmacytoma
5. Infection requiring systemic antibiotic therapy or other serious infection ≤ 14.0 days before initiating maintenance therapy.
6. Patients who have received systemic treatment, ≤ 14.0 days before the first dose of maintenance therapy, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort
7. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal (GI) procedure that could interfere with the oral absorption or tolerance of treatment

[2]A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).menses at any time in the preceding 24 consecutive months).

## 2.4. Treatment Plan

Patients meeting the eligibility criteria for transplant/enrollment will be treated with conditioning regimen of fludarabine, melphalan and bortezomib. GVHD prophylaxis consists of tacrolimus and methotrexate.

### 2.4.1. Conditioning Regimen (Fludarabine/Melphalan/Bortezomib)[113]

Patients will receive fludarabine 30 mg/m$^2$ (when creatinine clearance 40 – 70 mL/min, reduce to 24 mg/m$^2$) from Day -6 to Day -3, melphalan 70 mg/m$^2$ on Day -4 and Day -3 intravenously, and bortezomib on Day -3 at 1.3 mg/m$^2$ intravenously (Table 2.4.2). On Day 0, patients will receive the donor peripheral blood stem cells.

Dose of bortezomib will be determined based on the actual body surface area (BSA). See Section 2.4.1.1. for dosing guidelines for fludarabine and melphalan.

#### 2.4.1.1. Dosing for Melphalan, Fludarabine, and Methotrexate

The following guidelines should be utilized to determine the appropriate dosing for the administration of fludarabine, melphalan, and methotrexate.

For patients who weigh less than 125% of their ideal body weight (IBW), dosing should be based on actual body weight. Ideal and actual body weight units are in kilograms (kg), and calculations are based on gender. The calculation for IBW is explained in Table 2.4.2.

**Table 2.4.2 Calculation of IBW Based on Gender**

| | **Standard[1]** | **Metric[2]** |
|---|---|---|
| **Males** | IBW = 50kg + 2.3 kg/inch over 60” | IBW = 50kg + 2.3kg·[(height in meters– 1.52)/0.025] |
| **Females** | IBW=45.5kg +2.3kg/inch over 60” | IBW=4.5kg + 2.3kg·[(height in meters – 1.52)/0.025] |

[1]For patients shorter than 5ft, subtract 2.3 kg/inch.
[2]For patients shorter than 1.52 m, subtract 2.3kg for each 2.5 cm below 1.52 m.

AIBW = IBW + [(0.25) x (actual body weight – IBW)]

#### 2.4.1.2. Renal insufficiency dose adjustment for fludarabine

Patients with moderate renal impairment (creatinine clearance 40 – 70 mL/min) should receive reduced dose of fludarabine at 24 mg/m$^2$ (20% dose reduction). Fludarabine should not be administered to patients with severely impaired renal function (creatinine clearance < 40 mL/min).

**Table 2.4.3**

| | Day -6 | Day -5 | Day -4 | Day -3 | Day -2 | Day -1 | Day 0 |
|---|---|---|---|---|---|---|---|
| Fludarabine 30 mg/m$^2$ IV | X | X | X | X | | | |
| Melphalan 70 mg/m$^2$ IV | | | X | X | | | |
| Bortezomib 1.3 mg/m$^2$ IV | | | | X | | | |
| PBSC infusion | | | | | | | X |

2.4.2. GVHD Prophylaxis (Tacrolimus/Methotrexate)

A combination of tacrolimus and methotrexate will be administered for GVHD prophylaxis.

Tacrolimus will be administered beginning Day -3 of allogeneic HCT and will be continued for a minimum of 6 months. The initial dose should be calculated based on institutional guidelines to achieve an intravenous daily dose of 0.015 mg/kg/day. Subsequent doses are targeted to achieve whole blood levels between 5 and 10 ng/mL. When a patient is switched from IV to PO tacrolimus, the dose is increased by three- to four-fold to adjust for the lower bioavailability of oral compound to intravenous tacrolimus. Determinations of blood levels should be performed at least once weekly for the first 3 months. Dose reductions should be made if the toxicities are present or whole blood levels are above the recommended therapeutic range, following the institutional guidelines. Tacrolimus taper may begin 3 months post-allogeneic HCT in the absence of GVHD. Patients who are required to stop tacrolimus due to toxicity should be placed on another immunosuppressive agent according to institutional guidelines.

Methotrexate will be given at 5 mg/m$^2$/day IV on Days +1, +3, +6 and + 11 (a total of 4 doses). The Day +1 methotrexate should be administered no sooner than 24 hours after the completion of the stem cell infusion. See Section 2.4.1.2. for methotrexate dosing guidelines.

2.4.3. Donor Peripheral Blood Stem Cell Infusion

The target for CD34+ peripheral blood stem cell collection from matched donors will be 5 to 10 x $10^6$/kg of recipient body weight. Related donor peripheral blood stem cells will be mobilized with granulocyte-colony stimulating factor (G-CSF) according to institutional guidelines. For unrelated donors, National Marrow Donor Program (NMDP) protocols will be followed for stem cell mobilization and collection. T-cell replete stem cell grafts without manipulation will be used.

2.4.4. Randomization to Placebo or Ixazomib Maintenance Therapy

Prior to initiating therapy patients must meet the eligibility criteria outlined in section 2.3.3. If patients do not meet the criteria to proceed with maintenance at any time, they will continue to be followed per the protocol for the duration of the study.

Between Day +60 and Day +120 after allogeneic HCT, patients will be randomized to receive either ixazomib maintenance therapy or placebo. Maintenance therapy must begin within 7 days of randomization.

### 2.4.5. Ixazomib/Placebo Initiation

The starting doses of ixazomib and placebo are 3 mg, administered orally once a day on Days 1, 8, and 15 on a 28-day cycle. Only enough ixazomib and placebo for one cycle of therapy will be supplied to the patient each cycle according to randomization assignment. Assigned treatment will be administered for a maximum of 12 cycles (28-days/cycle).

Dosing will be in the morning at approximately the same time each day. Ixazomib and placebo capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of ixazomib or placebo is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up unless there is greater than 72 hours before the next 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. Patients who take more than the prescribed dose of ixazomib or placebo should be instructed to seek emergency medical care if needed and contact study staff immediately.

Dose escalation and de-escalation on both treatment arms will be performed depending on tolerability or development of adverse reactions (Sections 2.4.5.2 and 2.4.5.3). Subjects will be evaluated for adverse events (AEs) at each visit using the NCI CTCAE criteria v4.0. Subjects experiencing AEs may need study treatment modifications (per Treatment Modification Guidelines, Table 2.4.3). The planned dose of oral ixazomib and placebo ranges from 2 mg per day to 4 mg per day. All dosing is on Days 1, 8, and 15 on a 28-day cycle.

#### 2.4.5.1. Record of Administration

Accurate records will be kept of all ixazomib administration (including prescribing and dosing) and entered in the source documents.

#### 2.4.5.2. Dose Escalation in the Absence of Toxicities

If no toxicity occurs after completing 3 cycles of ixazomib or placebo at 3 mg/day on Days 1, 8, and 15 of a 28-day cycle, the dose of ixazomib or placebo will be escalated to the next dose level of 4 mg/day on Days 1, 8, and 15 of a 28-day cycle (Table 2.4.3). The dose of ixazomib or placebo will be maintained at 4 mg PO on Days 1, 8, and 15 of a 28-day cycle until the patient reaches a total of 12 cycles as long as no significant toxicities are encountered.

If the patient experiences toxicity requiring reduction of ixazomib or placebo dose, this level will be maintained for all subsequent cycles unless further toxicities occur. No dose re-escalation is permitted.

**TABLE 2.4.4: Ixazomib/Placebo Dose Reduction Steps**

| | |
|---|---|
| Dose Level 1 | 4 mg PO daily on Days 1, 8, and 15 of a 28-day cycle |
| Dose Level 0 (starting dose) | 3 mg PO daily on Days 1, 8, and 15 of a 28-day cycle |
| Dose Level -1 | 2.3 mg PO daily on Days 1, 8, and 15 of a 28-day cycle |
| Off Maintenance | Patient should discontinue all maintenance treatment |

2.4.5.3. Ixazomib or Placebo Dose Reduction

Ixazomib and placebo dose modifications (Table 2.4.4) will be made according to the Treatment Modification Guidelines (Table 2.4.5). Grading of toxicity will be based on CTCAE version 4.0.

2.4.5.4. Initiation of a New Cycle of Ixazomib or Placebo

A new course of maintenance may begin on the scheduled Day 1 of a new cycle if:

- The ANC is $\geq 1{,}000/mm^3$ (growth factor use is permitted)
- The platelet count is $\geq 75{,}000/mm^3$, without platelet transfusion within the last 3 days
- No $\geq$ grade 2 visceral (gut or liver) acute GVHD. No $\geq$ Grade 3 any acute GVHD
- No severe chronic GVHD
- Not receiving systemic chronic GVHD therapy in addition to steroids and calcineurin inhibitors for treatment of mild to moderate chronic GVHD
- Any other drug related adverse event that may have occurred has resolved to $\leq$ grade 1 severity including drug related rash, allergic reaction/hypersensitivity or sinus bradycardis/other cardiac arrhythmia. (see Table 2.4.4)
- No suspected pregnancy
- Not receiving a prohibited therapy (see Section 2.5.11)

If these conditions are not met prior to Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of maintenance will not be initiated until the toxicity has resolved as described above. Following resolution of toxicities, the day that maintenance is initiated will be Day 1 of the new cycle.

If maintenance was stopped during the previous cycle and restarted with a one-level dose reduction and no subsequent interruptions were required, then that reduced dose level will be initiated on Day 1 of the new cycle.

If ixazomib or placebo dosing was omitted for the remainder of the previous cycle, or if a new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction when the toxicity has resolved as described above.

If unable to start new cycle for any reason (e.g. toxicity, surgery, medical condition) within 56 days of planned cycle, patient will discontinue maintenance and continue to be followed for all study endpoints.

### 2.4.5.5. Treatment Adherence

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Any unused ixazomib should be disposed of in accordance with Millennium'sguidelines.

**Table 2.4.5: Treatment Modifications Guidelines for Ixazomib or Placebo– Maintenance**

| **NCI CTCAE v4** | **Day 1** | **Day 8** | **Day 15** | **Day 16-28 of Cycle** |
|---|---|---|---|---|
| Desquamating (blistering) rash- any grade | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO |
| Erythema multiforme ≥ Grade 3 | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO | Discontinue IXAZOMIB or PLACEBO |
| Peripheral Neuropathy | New or worsening Grade 1 w/ pain or Grade 2; Hold IXAZOMIB or PLACEBO until toxicity has resolved to ≤ Grade 1without pain<br><br>New or worsening Grade 2 w/ pain or Grade 3; If the toxicity has resolved to ≤ Grade 1without pain, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4; Discontinue IXAZOMIB or PLACEBO | Grade 1 w/ pain or Grade 2; Hold IXAZOMIB or PLACEBO until toxicity has resolved to ≤ grade 1without pain<br><br>Grade 2 or Grade 3 w/ pain; If the toxicity has resolved to ≤ grade 1without pain, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4; Discontinue IXAZOMIB or PLACEBO | Grade 1 w/ pain or Grade 2; Hold IXAZOMIB or PLACEBO until toxicity has resolved to ≤ grade 1without pain<br><br>Grade 2 or Grade 3 w/ pain; If the toxicity has resolved to ≤ grade 1without pain, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4; Discontinue IXAZOMIB or PLACEBO | Grade 1 w/ pain or Grade 2; Hold IXAZOMIB or PLACEBO until toxicity has resolved to ≤ grade 1without pain<br><br>Grade 2 or Grade 3 w/ pain; If the toxicity has resolved to ≤ grade 1without pain, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4; Discontinue IXAZOMIB or PLACEBO |

| **NCI CTCAE v4** | **Day 1** | **Day 8** | **Day 15** | **Day 16-28 of Cycle** |
|---|---|---|---|---|
| Allergic reaction or hypersensitivity | Grade 2-3; Hold IXAZOMIB or PLACEBO<br><br>Grade 4: Discontinue IXAZOMIB or PLACEBO | Grade 2-3; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to ≤ grade 1, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4: Discontinue IXAZOMIB | Grade 2-3; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to ≤ grade 1, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4: Discontinue IXAZOMIB or PLACEBO | If the toxicity resolves to ≤ grade 1, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle.<br><br>Grade 4: Discontinue IXAZOMIB or PLACEBO |
| Glomerular filtration rate (Creatinine Clearance) | ≥ Grade 3; Hold IXAZOMIB or PLACEBO | ≥ Grade 3; Hold IXAZOMIB or PLACEBO<br><br>If creatinine clearance has improved to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | ≥ Grade 3; Hold IXAZOMIB<br><br>If creatinine clearance has improved to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If creatinine clearance improves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |
| Diarrhea (assessed as IXAZOMIB related) | ≥Grade 2; Hold IXAZOMIB or PLACEBO | ≥Grade 2; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to < grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | ≥Grade 2; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to < grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If the toxicity resolves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |
| Nausea (assessed as IXAZOMIB related) | ≥Grade 3; Hold IXAZOMIB or PLACEBO | ≥Grade 3; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | ≥Grade 3; Hold IXAZOMIB<br><br>If the toxicity has resolved to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If the toxicity resolves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |

| NCI CTCAE v4 | Day 1 | Day 8 | Day 15 | Day 16-28 of Cycle |
|---|---|---|---|---|
| Other non-hematologic toxicity (assessed as IXAZOMIB related) | ≥Grade 3; Hold IXAZOMIB or PLACEBO | ≥Grade 3; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity resolves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | ≥Grade 3; Hold IXAZOMIB or PLACEBO<br><br>If the toxicity resolves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If the toxicity resolves to ≤ grade 2, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |
| Neutropenia | ≥Grade 3 (ANC <1,000/mm$^3$); Hold IXAZOMIB or PLACEBO | ≥Grade 3 (ANC <1,000/mm$^3$); Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to ≤ grade 2 (ANC ≥ 1,000/mm$^3$), restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | ≥Grade 3 (ANC <1,000/mm$^3$); Hold IXAZOMIB or PLACEBO<br><br>If the toxicity has resolved to ≤ grade 2 (ANC ≥ 1,000/mm$^3$), restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If the toxicity resolves to ≤ grade 2 (ANC ≥ 1,000/mm$^3$), restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |
| Thrombocytopenia | Platelet count <75,000/mm$^3$; Hold IXAZOMIB or PLACEBO. | Platelet count <50,000/mm$^3$; Hold IXAZOMIB or PLACEBO<br><br>If the platelet count becomes ≥ 50,000/mm$^3$, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | Platelet count <50,000/mm$^3$; Hold IXAZOMIB or PLACEBO<br><br>If the platelet count becomes ≥ 50,000/mm$^3$, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. | If the platelet count becomes ≥ 75,000/mm$^3$, restart IXAZOMIB or PLACEBO at the next lower dose level in the next cycle. |

- Please consult NCI CTCAE v4.0 http://ctep.cancer.gov/reporting/ for complete **Grade** descriptions. The **"≥ Grade 3"** descriptions listed above are minimums.

### 2.4.6. Discontinuation of Maintenance

Treatment will continue until maximal duration of maintenance therapy is reached (twelve 28-day cycles), or the occurrence of any of the following events:

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator/Medical Monitor, may cause severe or permanent harm or which rule out continuation of maintenance study drug.
- Graft failure
- Development of grade III-IV acute GVHD
- Development of severe chronic GVHD

- Suspected pregnancy
- Inability to start planned cycle of ixazomib within 56 days of intended start date of each cycle.
- Major violation of the study protocol (to include subject noncompliance with study medications or protocol-specified procedures) at the discretion of the Protocol Officer.
- Withdrawal of consent
- The subject is lost to follow up
- Death
- Patient is unable to complete 12 cycles of maintenance therapy within 18 months of initiating maintenance therapy.
- Patient is receiving a prohibited therapy (see section 2.5.11)

## 2.5. Supportive Care

The following medications/supportive therapies are recommended during study participation, as applicable:

- The antiemetic regimen(s) will be based on institutional guidelines.
- Antimicrobials: Antibacterial, antiviral and antifungal prophylaxis during and after allogeneic HCT are recommended and will be administered based on local institutional guidelines. Consideration of prophylaxis for herpes zoster virus is recommended during maintenance therapy.
- For the prevention of hepatotoxicity, ursodiol will be given at 300 mg PO BID if < 90 kg, or 300 mg PO in a.m. and 600 mg PO in p.m. if ≥ 90 kg.
- Pain control with opioid analgesics and transfusional support will be provided per the institutional guidelines.

### 2.5.1. Tapering of GVHD Prophylaxis

Institutional practice should be followed for tapering immunosuppressive therapy in the absence of GVHD. However, the protocol recommends full immunosuppression for at least 3 months after stem cell infusion and taper completion by 6 months.

### 2.5.2. Donor Lymphocyte Infusions

Pre-emptive / Prophylactic administration of donor lymphocytes is not permitted in this protocol. Donor Lymphocyte infusion for treatment of falling donor cell chimerism must be approved by Protocol Chair or Officer before the procedure.

### 2.5.3. Management of Acute Graft-versus-Host Disease

**Grade I-II Acute GVHD** – Manage per institutional guidelines and per requirements for starting a new cycle of maintenance in section 2.4.5.4

**Grade III-IV Acute GVHD** – Discontinue study drug and treat per institutional guidelines.

### 2.5.4. Management of Chronic Graft-versus-Host Disease

**Mild or Moderate Chronic GVHD -** Manage per institutional guidelines. Study drug can be continued. If the patient requires systemic chronic GVHD therapy in addition to steroids and calcineurin inhibitors, then the study drug should be discontinued.

**Severe Chronic GVHD -** The study drug should be discontinued.

### 2.5.5. Management of other Toxicities

Management of toxicities will be done according to institutional guidelines. The approaches listed below are recommendations for patients without confirmed GVHD.

#### 2.5.5.1. 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.

#### 2.5.5.2. 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. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

#### 2.5.5.3. 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 first incidence of rash events occurred early during treatment, and there was no evidence of increased frequency of rash with prolonged exposure. The rash is often transient, self-limiting (resolves without medical intervention), 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 (eg, 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 (also, per protocol).

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 (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). The rare risks of Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), and pemphigus vulgaris have been reported in studies when ixazomib (or placebo) has been given in a multi-therapy regimen with concomitant medications known to cause rash and/or in the setting of confounding Treatment Emergent Adverse Events (TEAEs). These severe and potentially life-threatening or deadly conditions may involve 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. Study medications should be discontinued in the event of severe, potentially life-threatening rash.

#### 2.5.5.4. Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with clinical monitoring and 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 (see Table 6-2). 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.

#### 2.5.5.5. Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. 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 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

#### 2.5.5.6. 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.

#### 2.5.5.7. 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 decreased appetite. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

#### 2.5.5.8. Posterior Reversible Encephalopathy Syndrome

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.

#### 2.5.5.9. Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded. Transverse myelitis should be managed according to standard medical practice.

### 2.5.6. Progressive Multifocal Leukoencephalopathy (PML)

PML, which may be fatal, has occurred in less than 1% of oncology patients receiving ixazomib in combination with other cancer therapies. It is not known whether ixazomib causes PML; however, the possibility that ixazomib may have contributed to PML cannot be excluded. In the event of occurrence of PML, ixazomib should be discontinued and supportive care provided as needed.

### 2.5.7. Infection

Prophylaxis for infection and surveillance for infection, such as CMV reactivation, is per institutional guidelines. Investigators should consider the use of antiviral prophylaxis for herpes zoster during maintenance therapy.

### 2.5.8. Bisphosphonates

Intravenous bisphosphonates [either zolendronic acid or pamidronate according to institutional preference] may be initiated (or re-initiated) after the allogeneic hematopoietic cell transplantation according to local institutional practice.

### 2.5.9. Radiation Therapy

Radiation therapy is not permitted to be given in concurrence with the conditioning regimen or ≤ 14.0 days of initiating maintenance therapy. After transplantation, radiation may be administered for the following indications in the absence of disease progression after consultation with the Medical Monitor or one of the Protocol Chairs and a radiation oncologist:

1. Palliation of pain from bone lesions;
2. Prevention of pathologic fractures;
3. Relief of spinal cord compression or nerve root compression.

The radiation oncologist will determine dose and duration of radiation to be administered. Radiation to the liver or lungs should be avoided.

### 2.5.10. Immunizations Schedule

Immunizations should be administered according to institutional guidelines.

### 2.5.11. Post-Transplant Blood Products

Transfusion thresholds for blood product support should be per institutional guidelines. All blood products will be irradiated.

### 2.5.12. Prohibited Therapy

Concomitant use of other anti-cancer therapies, other anti-myeloma maintenance or investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

The following medications and procedures are prohibited during the maintenance therapy:

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. (Rationale: If there were to be a drug-drug interaction (DDI) with an inducer, ixazomib exposure woulddecreased):

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The following medicinal products and procedures are prohibited during the maintenance therapy:

- Excluded foods and dietary supplements include St. John's wort and Gingko biloba
- Any antineoplastic treatment except for drugs in this treatment regimen.
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before maintenance study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

## 2.6. Participants Risks

Recipients of allogeneic transplantation incur risks from pre-transplant conditioning and post transplant therapy, which must be weighed against the risk of the disease for which the transplant is prescribed. Major risks following transplantation include: 1) Pancytopenia: the intent of the allogeneic transplant is to replace the hematopoietic organ and decrease in hematopoiesis is a direct consequence of transplantation. Blood counts are temporarily low after the conditioning regimens and patients are transfusion dependents. During the pancytopenia period other complications may occur such as infection and bleeding diathesis. 2) Infection, which can be bacterial, viral, parasitic, or fungal. Often, these infections are life-threatening, particularly when caused by viral or fungal agents, and are associated with high mortality in the transplant population; 3) Graft Failure which is a result of non engraftment or loss of donor derived hematopoiesis after successful engraftment. Graft failure is an uncommon complication and is associated with a high risk of mortality; 4) End Organ Damage of one or more major organs may occur as a result of reactions to drugs (e.g., melphalan, antibiotics, anti-fungal medications, etc.), and as a result of destructive processes (e.g., infection, etc.) and may have a fatal outcome; 5) Relapse or Progression of MM may become active after transplantation; 6) GVHD: is a common complication of transplant and will be assessed as an outcome in this clinical trial. Patients may develop acute GVHD which most frequently occurs 100 days from the transplant (though it is not limited to this timeframe) and chronic GVHD which is mostly observed beyond 2 months from transplantation. GVHD may result in significant morbidity and mortality after transplantation; 7) Hepatic Veno-Occlusive Disease: is a complication related to the conditioning regimen and result in liver failure. This is an uncommon complication after transplants with reduced intensity conditioning as prescribed in this protocol; 8) Thrombotic Microangiopathy: is a drug induced complication often seen with calcineurin inhibitors used for GVHD prophylaxis. This complication is uncommon and it results in multi organ failure; 9) Second Primary Malignancy: exposure to chemotherapy increases the risk of development of second primary malignancies after transplantation. Additionally, patients with multiple myeloma have a higher risk of developing second primary malignancies. However, there is no evidence to date which suggests that exposure to proteasome inhibitors increases this risk; 10) Unknown Toxicities may occur in any individual patient due to multiple events and cumulative effects which may involve any and all organs, including the brain. Brain damage can result in severe loss of cognitive or neurologic function; and, 11) Death. These risks may or may not be increased by the post transplant therapies to be evaluated in this protocol.

### 2.6.1. Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 with BMT specific definitions when appropriate.

### 2.6.2. Bortezomib

To date, more than 436,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

Prescribing physicians and health care practitioners are referred to their locally approved product label for bortezomib regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of bortezomib therapy are presented in Appendix H. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 $mg/m^2$ twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

The most common bortezomib side effects include:

- Hematologic: anemia, neutropenia, thrombocytopenia, leucopenia, lymphopenia
- Neurologic: asthenia, dizziness, anxiety, syncope, headache, insomnia, fever, rigors, chills, peripheral neuropathy, and leukoencephalopathy, including reversible posterior leukoencephalopathy syndrome
- Pulmonary: cough, dyspnea, pleural effusion, pneumonitis, interstitial pneumonia, edema acute respiratory distress syndrome (ARDS)
- Cardiovascular: hypotension, tachycardia, atrial fibrillation, palpitation, congestive heart failure, bradycardia, atrial flutter, atrioventricular block, arrhythmia, cardiac failure, cardiac arrest, pericardial effusion, pericarditis
- Infectious: reactivations of herpes zoster, opportunistic infections
- Gastrointestinal: weight loss, decreased appetite, anorexia, constipation, dehydration, diarrhea, heartburn, dyspepsia, stomatitis, nausea, vomiting, ileus, GI perforation, acute pancreatitis
- Metabolic: hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia
- Renal: renal failure
- Neuromuscular and skeletal: arthralgias, back pain, bone pain, muscle cramp and myalgias
- Cutaneous: alopecia
- Miscellaneous: rash, hemorrhage, blurred vision, deafness, hepatitis, hyperbilirubinemia, peripheral edema

Other medical events of interest that are considered not causally related to bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of bortezomib may be found in the current Investigator's Brochure and Appendix H.

Bortezomib Precautions and Restrictions

It is not known what effects bortezomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit. *Postmenopausal is defined as the time after which a woman has experienced twelve (12) consecutive months without a menstrual period.*
- Surgically sterile
- If they are of childbearing potential (i.e., not postmenopausal or surgically sterile), agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 12 months post transplant, or agree to completely abstain from heterosexual intercourse. It is strongly recommended that at least 1 of these 2 methods be 'highly effective' (see Table 2.6.1).

**Table 2.6.1: Methods of Contraception**

| Highly Effective Methods | Other Effective Methods (barrier methods) |
|---|---|
| Intra-uterine devices (IUD) | Latex condom |
| Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants) | Diaphragm with spermicide<br>Cervical cap<br>Sponge |
| *If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.* | |

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to one (1) of the following:

- Practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of maintenance study drug, or completely abstain from heterosexual intercourse.

### 2.6.3. Fludarabine

Fludarabine (Flu) can lower the white blood cell count, in particular the CD4+ T-cells. The immunosuppression observed with the use of Flu increases the risk of infection, which can be life threatening. Hematopoietic suppression and immunosuppression are expected to occur as a direct effect of the antimetabolite. The most serious toxicity of Flu is neurological, and may consist of both peripheral neuropathy and encephalopathy. Toxicity can be manifested by fatigue, weakness, paresthesias, visual disturbances, somnolence and coma, that usually develop between 30 and 60 days from therapy. The incidence of serious neurological toxicity has been 36% in patients treated with $\geq 96$ mg/m$^2$ per day for 5-7 days,[131] a dose > 3 times higher than used in this protocol. Other adverse effects include fever, nausea, vomiting, diarrhea, stomatitis, skin rash, cough and idiopathic pneumonitis.

### 2.6.4. Melphalan

High dose melphalan is well tolerated by patients when they are supported with blood component transfusions, PBSC/marrow transplantation and broad-spectrum antibiotics. The duration of profound bone marrow suppression decreases with the use of PBSC infusion and colony stimulating factors. Gastrointestinal toxicity, which includes severe stomatitis, esophagitis and diarrhea, can be severe or life-threatening. Most patients receiving high dose melphalan will require parental narcotics for mucositis-related pain, IV hydration; may require IV alimentation and broad spectrum IV antibiotics. Despite moderate to severe symptoms in many patients, recovery is the norm, coincident with recovery of granulocytes. Other toxicities reported include pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

See the FDA-approved package insert for a comprehensive list of adverse events.

### 2.6.5. Methotrexate

The most frequently reported adverse reactions associated with methotrexate use as GVHD prophylaxis include:

- Neurologic: fever, dizziness, chills, undue fatigue
- Gastrointestinal: ulcerative stomatitis, nausea, abdominal distress, diarrhea
- Hematologic: leucopenia, anemia, and suppressed hematopoiesis (leading to infection)
- Miscellaneous: abnormal liver tests, kidney failure, and pulmonary complications after transplantation

### 2.6.6. Tacrolimus

Tacrolimus side effects include:

- Cardiovascular: hypertension

- Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think
- Gastrointestinal: nausea, vomiting
- Hematologic: microangiopathic hemolytic anemia, thrombocytopenia
- Endocrine and metabolic: hypomagnesemia, hypokalemia, hypocalcemia, hyperlipidemia
- Miscellaneous: unwanted hair growth, changes in vision, liver problems, reversible renal insufficiency, infections and post transplant lymphoproliferative disorders
- Reversible posterior leukoencephalopathy syndrome [RPLS]
- Posterior reversible encephalopathy syndrome [PRES] (headache, confusion, seizures, and vision loss caused by very high blood pressure that comes on quickly)

### 2.6.7. Ixazomib

Please refer to the current MLN9708 (ixazomib) Investigator's Brochure (IB).

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to bortezomib, which has a known safety profile. The most frequent AEs reported to date in the ongoing MLN9708 studies are noted in the IB and informed consent document (Appendix B). However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

MLN9708 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.[120,,,,,127]

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

The known anticipated risks of ixazomib are presented in the ixazomib investigator's brochure which can be found on the BMT CTN SharePoint Website (https://bmtctnsp.net/).

**Pregnancy**

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following criteria:

- Postmenopausal for at least 1 year before the screening visit, OR

- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception (see Table 2.6), at the same time, from the time of signing the informed consent form through 90 days after the last dose of maintenance study drug, AND
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of maintenance study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

## 2.7. Study Drug Supply

### 2.7.1. Melphalan, Fludarabine, Tacrolimus and Methotrexate

These drugs are commercially available agents and will be administered per local institutional guidelines.

### 2.7.2. Bortezomib

**Drug Supply, Preparation, Handling and Storage**:
Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol.

Vials containing lyophilized bortezomib for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush

eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single-use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within 8 hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more than 8 hours after reconstitution.

**Administration**:
Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may be treated on an outpatient basis, if possible.

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram or calculation. The dose should be calculated on the day of administration (Day -3 pre-transplant).

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single-use administration.

**Drug Ordering**:
Bortezomib will be supplied to participating centers from the BMT CTN 1302 Central Pharmacy. Refer to the BMT CTN 1302 Study Drug Guide for additional information regarding study drug supply and ordering, or contact the BMT CTN 1302 DCC Protocol Coordinator.

**Drug Accountability:**
Accountability for the drug at all study sites is the responsibility of the Principal Investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and disposal of the drug (if applicable) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

**Drug Destruction:**
Investigational bortezomib (expired or end of study) will be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

### 2.7.3. Maintenance Study Drug (Ixazomib and Placebo)

**Ixazomib Mechanism of Action**
Ixazomib is a boronate proteasome inhibitor that is a reversible inhibitor of primarily the chymotrypsin-like activity of the 20S proteasome.

**Human Safety of Ixazomib and Pharmacology**
Ixazomib has a shorter dissociation half-life compared to bortezomib and has demonstrated greater tissue penetration compared with bortezomib in preclinical studies. Ixazomib is orally available and has been shown to inhibit NF-kB activation. In vitro and in vivo studies have demonstrated antitumor activity in MM and other hematologic malignancies.

Oral ixazomib is rapidly absorbed and substantially bioavailable, it is rapidly hydrolyzed into MLN2238, the biologically active form. An analysis of four phase I monotherapy studies of IV and oral ixazomib showed that for twice-weekly dosing, the Day 1 and Day 11 extrapolated immediate post-IV bolus plasma concentration of MLN2238 (C0) was roughly dose proportional over the dose range (0.125 to 2.34 mg/m$^2$)[96]. In contrast, both the Day 1 and Day 11 dosing interval plasma concentration-time AUCs showed dose proportional increases only over the higher dose range (1 to 2.34 mg/m$^2$). There was approximately 3–4 fold accumulation of MLN2238 by Day 11 on the twice-weekly schedule. For weekly IV dosing of ixazomib, only lower dose levels had been studied by then (0.125 to 1.4 mg/m$^2$) but the PK behavior appeared to be similar to that for twice-weekly dosing, with the exception that MLN2238 accumulated to a lesser degree (approximately 2-fold). Following oral administration of ixazomib capsules, there was rapid absorption of MLN2238 ($T_{max}$ approximately 1 hr). At the doses studied to date (0.24 to 1.2 mg/m$^2$) for twice-weekly and weekly dosing of ixazomib, systemic exposures achieved with oral dosing were similar to those achieved with IV dosing on the same schedule, indicating that the oral bioavailability of MLN2238 is substantial.

In a population pharmacokinetic (PK) analysis of pooled data from 4 phase I studies, absolute bioavailability was estimated to be 62%[97]. Based on simulations using the final population PK model, there was no difference in concentration-time profile or exposures (AUC or $C_{max}$) between the BSA-based and the flat doses, supporting a switch from BSA-based dosing to flat dosing in all ongoing and planned clinical studies.

Maintenance therapy will be double-blinded and placebo capsules will be the same appearance and dosage as ixazomib. All the approaches described in Section 2.7.3 for ixazomib apply to placebo.

**Precautions and Handling:**
MLN9708 (ixazomib) is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling MLN9708 capsules.

**Packaging and Labeling:**
The maintenance study drug ixazomib will be provided by Millennium. Both maintenance study drugs will be blinded prior to shipment to the participating institution. They will be packaged and

labeled identically, with no drug identifying information. The packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 2.3, 3.0, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

**Availability (Ixazomib):**
Maintenance study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg ixazomib.

Hazardous agent; use appropriate precautions for handling and disposal.

**Availability (Placebo):**
Placebo will be supplied by Millennium as capsules of similar size, color, and shape to ixazomib. Like ixazomib, the placebo will be available in 2.3, 3.0, and 4.0 mg capsules.

**Preparation:**
For blistered material, the capsules are packaged in cold form foil-foil blisters with a paper backing for child-resistance. Both maintenance study drugs will be provided by Millennium and distributed to participating centers via the BMT CTN 1302 Central Pharmacy.

**Storage and Stability:**
Upon receipt at the investigative site, ixazomib or placebo (study drug) should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated at 2°C to 8°C (36°F to 46°F) and must not be frozen. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, study drug capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations.

Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated at 2°C to 8°C (36°F to 46°F) for the duration of each cycle. Patients should be instructed to return their empty blister packs 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 as an excursion and should be dealt with on a case-by-case basis.

Because study drug is an investigational agent, it should be handled with due care.

Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be

harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during clean-up and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of study drug, including that study drug is to be taken as intact capsules.

**Administration:**
All protocol-specific criteria for administration of maintenance study drug must be met and documented before drug administration. Maintenance study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of study drug dose (see Section 2.4.5.5).

Patients should be instructed to swallow study drug capsules whole, with water, and not to break, chew, or open the capsules. Maintenance 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. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

If a dose of study drug is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. 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.

**Drug Ordering**:
Maintenance study drug (ixazomib and placebo) will be shipped to participating centers from the BMT CTN 1302 Central Pharmacy. Patient-specific supplies of maintenance study drug will be distributed to sites in capsules of different strengths according to the prescribed dose. The drug will be provided in single cycle blister packs, and the central pharmacy will ship three cycles (one quarter) of drug per order. Upon completion of a cycle, centers need to confirm dosage for the subsequent cycle and request a new shipment of a study drug if a dose adjustment is necessary. Centers will need to request maintenance study drug at the end of every quarter. Refer to the BMT CTN 1302 Study Drug Guide for additional information regarding study drug supply and ordering, or contact the BMT CTN 1302 DCC Protocol Coordinator.

**Drug Accountability:**
Accountability for study drug at all study sites is the responsibility of the Principal Investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and return or disposal of the drug will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

**Drug Destruction:**
Study drug (expired or end of study) will be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

## 2.8. Blinding Procedures

Assignment to ixazomib or placebo will be done according to computer-based randomization results. All treatment assignments will be blinded to study investigators, physicians, investigational pharmacists, and patients. The randomization assignment will determine patient-specific supplies for the entire maintenance period and it will be identified according to the patient's and center's identification numbers.

## 2.9. Unblinding Procedures

Maintenance study drug will be un-blinded for all patients upon study analyses or if deemed appropriate by the DSMB. Request for un-blinding for unique situations will be reviewed by the study team and DSMB in a case by case basis.

Unblinding of maintenance study drug assignment will be considered in cases that impact safety to patients. Any investigator who wants to request an unblinding prior to protocol-defined study-wide unblinding should send their request to BMTCTN1302unblinding@emmes.com. Requests should include the following information:

- Name of Investigator along with his/her telephone number and email address
- Name of institution
- Participant ID
- A detailed description of the issue surrounding the request for unblinding.

Upon its receipt, the unblinding request will be discussed, and any additional information needed will be obtained from the investigator who initiated the request. A response will be provided within one business day following review by the Protocol Chair(s) and/or Protocol Officer, DSMB, and NHLBI, where applicable.

In case of unblinding, the study participant might be taken off protocol directed interventions. Recommendations on whether the study interventions will continue after unblinding will be dependent on individual cases and deliberated by the DSMB.

# CHAPTER 3

# 3. STUDY ENDPOINTS AND DEFINITIONS

## 3.1. Definition of Disease Status

Patients' disease status at each data collection period will be evaluated based on the International Uniform Response Criteria. Until disease progression, all disease classifications are relative to the patient's disease status prior to allogeneic transplant (i.e. study entry). At time of disease progression, disease classifications are relative to the patient's best response since time of study entry.

### 3.1.1. International Uniform Response Criteria

Response and disease progression assessments will follow the International Uniform Response Criteria. For additional information on assessing response in patients with plasma cell leukemia see Appendix A.

### 3.1.2. Response Categories

**Stringent Complete Response (sCR):**
sCR requires, in addition to CR (defined below), all of the following:

- Normal free light chain ratio (FLC).
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[a].

**Complete Response (CR):**
CR requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation. The presence of new monoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed.
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)*.
- Disappearance of soft tissue plasmacytomas.

**If not clinically indicated, radiographs are not required to document CR.*

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial responses (see below), providing the remaining criteria satisfy the requirements for partial response. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

**Very Good Partial Remission (VGPR)**
VGPR requires, in addition to PR (defined below), all of the following:

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis

OR

- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein < 100 mg/24hrs

For free light chain only disease, VGPR requires a 90% reduction of involved light chain.

For patients without measurable monoclonal paraprotein at the time of relapse or progression, VGPR requires a 90% reduction in the difference between involved and uninvolved free light chain level, and < 5% plasma cells in the bone marrow.

**Partial Response (PR)**
PR requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to < 200 mg/24 hours in light chain disease.
- If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio,
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%,
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas if present at baseline (by radiography or clinical examination).

**Stable Disease (SD)**

- Patients who do not meet criteria for sCR, CR, VGPR, partial response or progressive disease (section 3.1.1.2) are considered to have stable disease (SD).

3.1.3. Progressive Disease (PD)

**Disease Progression (PD)**
Progression from CR or sCR requires one or more of the following:

- A reappearance of serum monoclonal paraprotein, with a level of at least 0.5 g/dL.
- 24-hour urine protein electrophoresis with at least 200 mg paraprotein/24 hours.
- Abnormal FLC levels of > 10 mg/dl, only in patients without measurable paraprotein in the serum and urine.
- At least 10% plasma cells in a bone marrow aspirate or on trephine biopsy.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca > 11.5 mg/dL or > 2.8 mmol/L) not attributable to any other cause.

**Progressive Disease (PD)**
For patients not in CR or sCR, progressive disease requires one or more of the following measured from the lowest possible value:

- > 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- > 25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- Absolute increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl), only in patients without measurable paraprotein in the serum and urine.
- > 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of a compression fracture does not exclude continued response and may not indicate progression.
- Development of hypercalcemia (corrected serum Ca > 11.5 mg/dL or > 2.8 mmol/L) not attributable to any other cause.

## 3.2. Primary Endpoint

The primary endpoint is to compare progression-free survival as a time to event endpoint from randomization between patients randomized to ixazomib and placebo maintenance in high risk multiple myeloma. Patients are considered a failure of the primary endpoint if they die or suffer from disease progression as defined above or if they initiate non-protocol anti-myeloma therapy. The time to this event is the time from randomization to progression, death, or initiation of non-protocol anti myeloma therapy whichever comes first.

## 3.3. Secondary Endpoints

### 3.3.1. Acute GVHD

Acute GVHD will be graded according to the BMT CTN MOP. The time of onset of acute grades II-IV GVHD and grades III-IV GVHD will be recorded, as well as the maximum grade achieved.

### 3.3.2. Chronic GVHD

Chronic GVHD will be scored according to the BMT CTN MOP. The time of onset of limited and extensive chronic GVHD will be recorded.

### 3.3.3. Response to Treatment

The event is the best response (sCR, CR, VGPR or PR) after randomization. Best response after allogeneic transplant will also be described.

### 3.3.4. Disease Progression

Disease progression as defined above will be the event of this outcome. Patients with prior CR will only be considered an event if they meet the progression criteria, disease relapse (i.e reappearance of original M spike) below the levels defined as progression will not be considered an event for this outcome.

### 3.3.5. Treatment-Related Mortality (TRM)

The event for TRM is any death that occurs in the absence of post-allogeneic HCT progression. Multiple myeloma progression is considered a competing risk for this event.

### 3.3.6. Overall Survival

Time to overall survival is defined as the time to death from any cause or for surviving patients, to last follow-up. The event for overall survival is death from any cause and surviving patients will be censored at the last date of follow-up.

### 3.3.7. Toxicity

All grades $\geq 3$ toxicities according to CTCAE, version 4 will be tabulated for each intervention arm. The proportion of patients developing grade $\geq 3$ AE across intervention arms will be compared.

### 3.3.8. Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each intervention arm. All Grade 2 and 3 infections will be reported according to the BMT CTN MOP.

### 3.3.9 Rate of Non-Randomization

The proportion of patients not achieving randomization by Day 120 post-allogeneic HCT will be described.

### 3.3.10 Health Quality of Life

The FACT-BMT version 4.0 instrument is comprised of a general core questionnaire: the FACT-G, which evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The MOS SF-36 instrument is a general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, and Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. This scale has been widely applied in a variety of outcome studies and is being used in this protocol as a generic measure of quality of life. To facilitate comparison of the results with published norms, the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be used as the outcome measures in summarizing the SF-36 data.

HQL will be described from pre-transplant to last follow up at 24 months post transplant. Additionally, HQL will be compared between the maintenance arms utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool (SF-36). The questionnaires will be scored according to standard procedures. The self-report questionnaires will be completed prior to transplant, prior to randomization, 6 months after maintenance initiation, at time of maintenance completion and 24 months after transplant. Comparisons of quality of life will be done between maintenance arms at each of the time points after randomization. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial.

### 3.3.11 Post-Transplant Endpoints

Estimates for the primary and key secondary endpoints for each arm of maintenance therapy will be described post transplant.

# CHAPTER 4

# 4. PATIENT REGISTRATION, ENROLLMENT AND EVALUATION

## 4.1. Enrollment Procedures

Enrollment onto the BMT CTN 1302 trial is a multi-step process and must be conducted by an authorized user at the clinical center. The following must be completed, in the below order, to enroll a patient onto trial:

1. Demographics Form
2. Segment 0 Enrollment Form – documents the patient's consent to participate in the trial
3. HLA Form – documents that the patient-donor HLA match score meets protocol requirements
4. Segment A Enrollment Form – documents that the patient meets the protocol's eligibility criteria (Section 2.3.1. through Section 2.3.3.)

A patient is not considered enrolled onto the trial, thus no protocol-prescribed treatment can be initiated, until the Segment A Enrollment Form is successfully saved and a confirmation screen is provided indicating the enrollment was successful. Once the patient is enrolled, the Transplant Form must be completed in order to populate a visit schedule in the Forms Grid.

After the patient has adequately recovered from their transplant, he or she will be screened for eligibility for the randomized maintenance portion of the trial. If the patient is found to be eligible, the Segment B Enrollment Form must be completed between 60 and 120 days post-transplant to document that the patient meets the maintenance eligibility criteria (Section 2.3.4. through Section 2.3.5.). Successfully saving this form randomizes the patient. Maintenance study drug cannot be ordered until the Segment B Enrollment Form is completed and a confirmation screen with a randomization assignment is provided.

Refer to the BMT CTN 1302 Forms Guide for further guidance on the enrollment procedures and forms completion.

## 4.2. Study Monitoring

### 4.2.1. Follow-Up Schedule

The follow-up schedule for study visits post transplant and post initiation of maintenance are outlined below in Tables 4.2.1a and 4.2.1b, respectively. The follow-up schedule is the intended schedule; however, the date of the follow-up evaluations may vary due to delays in treatment or treatment interruption related to Adverse Events and toxicities. The visit window for the scheduled evaluations is included in Tables 4.2.1a and 4.2.1b. The follow up period is 2 years post-transplant, however there will be an extended reporting period for second primary malignancies (SPMs), which ends once all patients have completed 2 years of follow up. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the BMT CTN 1302 Forms Guide.

**Table 4.2.1a: Follow-Up Schedule**
**Post-Transplant/Prior to Maintenance**

| Study Visit | Target Day Post Transplant |
|---|---|
| Baseline | ≤ 42 days prior to transplant |
| 1 week | 7 ± 2 days |
| 2 week | 14 ± 2 days |
| 3 week | 21 ± 2 days |
| 4 week | 28 ± 2 days |
| 5 week | 35 ± 2 days |
| 6 week | 42 ± 2 days |
| 7 week | 49 ± 2 days |
| 8 week | 56 ± 2 days |
| 9 week | 63 ± 2 days |
| 10 week | 70 ± 2 days |
| 11 week | 77 ± 2 days |
| 12 week | 84 ± 2 days |
| 13 week | 91 ± 2 days |
| 14 week | 98 ± 2 days |
| Day 100[1,2] | 100 ± 7 days |
| Day 120[1,2] | 120 ± 7 days |

**[1]** Patients that proceed to maintenance therapy prior to Day 100 will begin to follow the study schedule outlines in table 4.2.1b: Follow-Up Schedule Post-Maintenance.

**[2]**If the pre-randomization visit falls within ± 7 days of visit 100 or visit 120 the assessments can be conducted during the same visit.

**Table 4.2.1b: Follow-Up Schedule Post- Maintenance for All Randomized Patients**

| Study Visit | Target Day Post-Maintenance[1] |
|---|---|
| Baseline (Pre-maintenance) | ≤ 14 days pre-maintenance |
| Cycle 1[2] | Day 1 ± 7 days |
| Cycle 2[2] | Day 29 ± 7 days |
| Cycle 3 | Day 57 ± 7 days |
| Cycle 4 | Day 85 ± 7 days |
| Cycle 5 | Day 113 ± 7 days |
| Cycle 6 | Day 141 ± 7 days |
| Cycle 7 | Day 169 ± 7 days |
| Cycle 8 | Day 197 ± 7 days |
| Cycle 9 | Day 225 ± 7 days |
| Cycle 10 | Day 253 ± 7 days |
| Cycle 11 | Day 281 ± 7 days |
| Cycle 12 | Day 309 ± 7 days |
| 28-day follow up after last dose | Day 339 ± 7 days (28 days after last dose) |

**1** The date of the follow-up evaluations may vary due to delays in treatment or treatment interruption related to adverse events and toxicities.
[2] Patients will be followed weekly for cycles 1 and 2, and monthly otherwise

**Table 4.2.1c: Follow-Up Schedule After Day 120 Post-Transplant for Non-Randomized Patients[1]**

| Study Visit | Target Day Post Transplant |
|---|---|
| 6 months post transplant | Day 180 ± 7 days |
| 12 months post transplant | Day 365 ± 7 days |
| 18 months post transplant (18T) | Day 540 ± 14 days |
| 24 months post transplant (24T) | Day 730 ± 14 days |

[1]All patients must be followed for SPMs until the last enrolled patient has completed 2 years of follow up.

**Table 4.2.1d: Follow-Up Schedule Endpoint Assessments for Randomized Patients[1]**

| Endpoints | Days From Transplant |
|---|---|
| 18 months post transplant (18T) | Day 540 ☐14 days |
| 24 months post transplant (24T) | Day 730 ☐14 days |

[1]All patients must be followed for SPMs until the last enrolled patient has completed 2 years of follow up.

## 4.3. Patient Evaluations

### 4.3.1. Pre-Transplant Evaluations and Requirements

The following observations will be made < **six weeks before enrollment:**

1. History and physical examination, height and weight
2. Karnofsky performance score
3. HCT- Specific Comorbidity Index score.
4. CBC with differential and platelet count, bilirubin, alkaline phosphatase, AST and ALT
5. Estimated creatinine clearance, using the Cockcroft-Gault formula and actual body weight.
6. Infectious disease markers to include: CMV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.
7. EKG and LVEF (may be performed < 12 weeks before enrollment).
8. Pulmonary function tests, including DLCO and FEV1 (may be performed < 12 weeks before enrollment).
9. HLA Typing (donor and recipient) as described in Chapter 2 (if not already performed).
10. Pregnancy test per institutional practices for females of child-bearing potential (i.e., not postmenopausal or surgically sterile as per Section 2.6.2). **NOTE: pregnancy test must be performed ≤ 14 days before enrollment**
11. Laboratory Disease Evaluation:
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24 hour urine collection to determine protein excretion, urine electrophoresis (UPEP).
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC)
12. Skeletal bone survey to include cranium, axial skeleton and proximal long bones
13. 12-lead electrocardiogram (ECG)

### 4.3.2. Evaluations after Enrollment and Prior to Transplant

The following evaluations must be completed after enrollment in to BMT CTN 1302 and prior to transplant.

1. Health-related quality of life assessment, SF-36 and FACT-BMT (for English and Spanish speaking patients only).
2. Optional Samples for Future and Ancillary Research (Appendix C)
    a. Peripheral Blood: single 36 mL sample of your blood (approximately 7 teaspoons) will be collected for future research and immune reconstitution assessment
    b. Bone Marrow: bone marrow aspirate (10 mL) collection for future research and MRD assessment
3. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are indicated to assess disease status prior to transplantation

### 4.3.3. Post-Transplant Evaluations and Requirements

The following evaluations are after the allogeneic HCT. These evaluations will occur **as indicated below and in Table 4.3.1.**

1. Physical examination and appropriate lab evaluations to assess GVHD and other morbidity weekly starting at Day 7 post-transplant through Day 98 post-transplant, then at Day 120 post-transplant.
2. Assessment for Toxicities at Days 28, 56 and 100 post-transplant
3. CBC with manual differential to be performed weekly from Day 0 until engraftment. CBCs will be performed per institutional guidelines from the time of engraftment through randomization. post transplant.
4. Liver Functions and Blood Chemistries: total bilirubin, alkaline phosphatase, AST, ALT per institutional guidelines prior to randomization.
5. Sorted or unsorted chimerism analysis (peripheral blood or bone marrow) at Days 56 and 100 post-transplant[1]. Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3, CD33, or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points.
6. Laboratory Disease Response Assessment required at Days 56 and 120 post-transplant
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24-hour urine collection to determine protein excretion, urine electrophoresis (UPEP).

[1]The chimerism analyses at Day 180 and 365 should align with the chimerism analyses required at Cycles 3 and 9 of maintenance therapy. See table 4.3.2.

d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.

e. Serum free light chain ratios (FLC)

7. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients.
8. Optional Samples for Future and Ancillary Research (Appendix C)
    a. Peripheral Blood: single 36 mL sample of blood (approximately 7 teaspoons) will be collected for future research and immune reconstitution assessment at Day 28 post-transplant. For patients who delayed the initiation of maintenance or do not proceed to maintenance, blood collection will be done at Day 100, 180 and 365 post transplant.
9. Data on occurrence of infections recorded as per BMT CTN MOP.

4.3.4. Pre-Maintenance Evaluations and Requirements

The following evaluations to determine eligibility for randomization to maintenance therapy will be done **≤ 14 days prior to initiation of maintenance therapy (see Table 4.3.2).** If found eligible, **randomization must occur ≤ 7 days prior to initiation of maintenance.**

1. Physical examination and appropriate lab evaluations to assess GVHD and other morbidity
2. Karnofsky performance score
3. CBC with differential, platelet count
4. Estimated creatinine clearance, using the Cockcroft-Gault formula and actual body weight.
5. Liver Functions and blood chemistries: total bilirubin, alkaline phosphatase, AST, ALT
6. Thyroid Stimulating Hormone (TSH)
7. Pregnancy test, serum HCG (sensitivity of at least 50 mIU/mL).
8. Laboratory Disease Evaluation[2]:
    - Quantitative serum immunoglobulin levels.
    - Serum protein electrophoresis (SPEP).
    - 24-hour urine collection to determine protein excretion, urine electrophoresis (UPEP).
    - Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    - Serum free light chain ratios (FLC)
9. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients.
10. Skeletal bone survey to include cranium, axial skeleton and proximal long bones

[2] Laboratory Disease Evaluations performed at Day 60 and Day 120 post-transplant can be used as evaluations prior to maintenance therapy if they are ≤ 14 days prior to the initiation of maintenance therapy.

11. Sorted or unsorted chimerism analysis (peripheral blood or bone marrow). The chimerism analysis technique (sorted or unsorted) is at the discretion of the transplant center but must be utilized consistently while on maintenance study drug.
12. Assessment for Toxicities
13. Health-related quality of life assessment, SF-36 and FACT-BMT (for English and Spanish speaking patients only).
14. Optional Samples for Future and Ancillary Research (Appendix C)
    a. Peripheral Blood: single 36 mL sample of blood (approximately 7 teaspoons) will be collected for future research and immune reconstitution assessment
    b. Bone Marrow: bone marrow aspirate (10 mL) collection for future research and MRD assessment

4.3.5. Evaluations During Maintenance Therapy

Upon initiation of maintenance, weekly laboratory monitoring and GVHD assessment is required during Cycles 1 and 2, within a window of ± 2 days. Laboratory monitoring is required once every cycle for all cycles thereafter. Patient visits are mandatory for planned Cycles 1-12 and 28 days after the last dose of maintenance study drug, unscheduled visits and laboratory monitoring may take place as needed.

The following required observations are after initiation of maintenance therapy. These evaluations will occur **as indicated below and in Table 4.3.2.**

1. Physical examination and appropriate lab evaluations to assess acute and chronic GVHD and other morbidities weekly from 7 days after the initiation of maintenance until 60 days; after 60 days they are required once every cycle.
2. CBC with differential, platelet count weekly for Cycle 1 and monthly otherwise.
3. Laboratory Disease Evaluation required every 3 months:
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24-hour urine collection to determine protein excretion, urine electrophoresis (UPEP).
    d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.
    e. Serum free light chain ratios (FLC)
4. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients.
5. Thyroid Stimulating Hormone (TSH) to be obtained every three months.
6. Skeletal Survey to include cranium, axial skeleton and proximal long bones is required ≤ 28 days of the last dose of maintenance, but otherwise may be performed as clinically indicated during the course of the study at the discretion of the transplant physician.

7. Sorted or unsorted chimerism analysis (peripheral blood or bone marrow) every six months during treatment with maintenance study drug and as otherwise clinically indicated, at the discretion of the transplant physician. The chimerism analysis technique (sorted or unsorted) is at the discretion of the transplant center but must be utilized consistently while on maintenance study drug.
8. Assessment and appropriate lab evaluations for toxicities at Cycles 1, 2, 3, 4, 6, 9, 12 and ≤ 28 days after the last dose of maintenance study drug.
9. Health-related quality of life assessment, SF-36 and FACT-BMT (for English and Spanish speaking patients only) after Cycle 6, ≤ 28 days after the last dose of maintenance study drug and at 2 years post-transplant (24T).
10. Accurate records will be kept of all maintenance study drug prescription and administration. No more than one cycle of maintenance study drug will be dispensed to the patient at a time
11. Optional Samples for Future Research collected at the timepoints listed below and in table 4.3.2.
    a. Peripheral Blood: single 36 mL sample of blood (approximately 7 teaspoons) will be collected for future research and immune reconstitution assessment at cycles 2 (~100 days post-transplant), 5 (~180 days post transplant), 10 (~1 year post-transplant) and within 28 days of the last dose of maintenance study drug.
    b. Bone Marrow: bone marrow aspirate (10 mL) collection for future research and MRD assessment will occur within 28 days of the last dose of maintenance study drug

4.3.6. Evaluations for Non-Randomized Patients

Patients who are not randomized for any reason should be followed at the time points outlined in tables 4.2.1A and 4.2.1C.

The following evaluations will occur after Day 120 post transplant for non-randomized patients. These evaluations will occur **as indicated below and in Table 4.3.3.**

1. Physical examination and appropriate lab evaluations to assess acute and chronic GVHD at 6 months and 12 months.
2. CBC with differential, platelet count at 6 months, 12 months, 18 months, and 2 years post- transplant.
3. Laboratory Disease Evaluation required at 6 months, 12 months, 18 months, and 2 years post-transplant:
    a. Quantitative serum immunoglobulin levels.
    b. Serum protein electrophoresis (SPEP).
    c. 24-hour urine collection to determine protein excretion, urine electrophoresis (UPEP).

d. Immunofixation of urine and serum protein regardless of SPEP and UPEP results.

e. Serum free light chain ratios (FLC)

4. Bone Marrow Evaluation: unilateral bone marrow biopsy and aspirate are required only to confirm CR in patients.
5. Skeletal bone survey to include cranium, axial skeleton and proximal long bones at 18 months and 2 years post-transplant.
6. Assessment for toxicities at 6 months, 12 months, 18 months, and 2 years post-transplant.
7. Health-related quality of life assessment, SF-36 and FACT-BMT (for English- and Spanish-speaking patients only) at 2 years post-transplant.

## Table 4.3.1: Patient Clinical Assessments (Pre/Post-Transplant)

| Study Assessments/ Testing | Baseline | Weeks Post Transplant | | | | | | | | | | Days Post Transplant | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10-14 | 100 | 120 |
| History, physical exam, weight and height | X | | | | | | | | | | | | |
| Karnofsky performance status | X | | | | | | | | | | | | |
| HCT-Specific Comorbidity Index score | X | | | | | | | | | | | | |
| HLA typing (donor and recipient) | X | | | | | | | | | | | | |
| CBC[1], differential, platelet count, and blood chemistries[2] | X | X | X | X | X | X | X | X | X | X | | X | X |
| Estimated Creatinine Clearance[3] | X | | | | | | | | | | | | |
| Infectious disease markers[4] | X | | | | | | | | | | | | |
| EKG and LVEF[5] | X | | | | | | | | | | | | |
| DLCO and FEV1[5] | X | | | | | | | | | | | | |
| Pregnancy test[6] | X | | | | | | | | | | | | |
| Quantitative serum immunoglobulins[11] | X | | | | | | | | X | | | | X |
| SPEP and immunofixation[11] | X | | | | | | | | X | | | | X |
| 24 Hour Urine for UPEP, protein excretion and immunofixation[11] | X | | | | | | | | X | | | | X |
| Serum free light chain ratio[11] | X | | | | | | | | X | | | | X |
| Bone marrow aspirate and biopsy[11] | X[12] | | | | | | | | X[7] | | | | X[7] |
| Optional blood sample for immune reconstitution and future research | X[12] | | | | X[10] | | | | | | | X[10] | |
| Optional bone marrow aspirate for MRD and future research [13] | X[12] | | | | | | | | | | | | |
| Skeletal Survey | X | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | |
| Health-Related Quality of Life[14] | X[12] | | | | | | | | | | | | |
| Chimerism[8] | | | | | | | | | X | | | X | |
| GVHD assessment | | X | X | X | X | X | X | X | X | X | X | | X |
| Toxicity assessment[9] | | | | | X | | | | X | | | X | |

**[1]** CBC with manual differential to be performed weekly from Day 0 until engraftment. CBCs will be performed per institutional guidelines from the time of engraftment through randomization.
**[2]** Blood chemistries include: bilirubin, alkaline phosphatase, AST and ALT. Blood chemistries performed per institutional guidelines through randomization.
**[3]** Estimated creatinine clearance is calculated using the Cockcroft-Gault formula and actual body weight.
**[4]** Infectious disease titers include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.
**[5]** May be performed within 12 weeks of enrollment
**[6]** Pregnancy test must be performed $\leq$ 14 days from enrollment. Pregnancy test is required for females of child-bearing potential and may be performed per institutional practices.
**[7]** Bone Marrow aspirate and biopsy required only to confirm CR in patients
**[8]** Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points.
**[9]** The toxicity assessment will include a review of **all** toxicities experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC.
**[10]** Peripheral blood for future research will be collected at Day 28 post-transplant. For patients who are delayed in initiating maintenance or not eligible to start maintenance additional blood collection for future research will be done at Days 100, 180 and 365.
[11] Myeloma response assessment for patients who are not randomized will be repeated at day 120 post transplant and every 6 months until completion of study period (2 years post transplant)
[12] These assessments should be performed after enrollment on BMT CTN 1302 through the AdvantageEDC system but prior to transplant.
[13] Minimial residual assessment will be done in bone marrow aspirate centrally at Roswell Park Cancer Institute. See Appendix C for procedures and Appendix L for details.
[14] English- and Spanish-speaking patients only.

## Table 4.3.2: Patient Clinical Assessments for Randomized Patients (Pre/Post-Maintenance)

| **Study Assessments/Testing[1]** | ≤ 14 days prior to initiation of maintenance | Cycle (28 days/cycle) | | | | | | | | | | | | | Days post transplant[2] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Follow Up | 18T | 24T |
| Karnofsky performance status | X | | | | | | | | | | | | | | | |
| CBC, differential, platelet count, and blood chemistries[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| TSH | X | | | X | | | X | | | X | | | X | | | |
| Estimated Creatinine Clearance[4] | X | | | | | | | | | | | | | | | |
| Pregnancy test (serum HCG (sensitivity of at least 50 mIU/mL)) | X | | | | | | | | | | | | | | | |
| Quantitative serum immunoglobulins | X | | | X | | | X | | | X | | | X | X | X | X |
| SPEP and immunofixation | X | | | X | | | X | | | X | | | X | X | X | X |
| 24 Hour Urine for UPEP, protein excretion and immunofixation | X | | | X | | | X | | | X | | | X | X | X | X |
| Serum free light chain ratio | X | | | X | | | X | | | X | | | X | X | X | X |
| Bone marrow aspirate and biopsy | X[5] | | | X[5] | | | X[5] | | | X[5] | | | X[5] | | | |
| Skeletal Survey[6] | X | | | | | | | | | | | | | X | X | X |
| Chimerism[7] | X | | | | | | X | | | | | | X | | | |
| Chronic and Acute GVHD assessment[8] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Toxicity assessment[9] | X | X | X | X | X | | X | | | X | | | X | X | X | X |
| Health-Related Quality of Life[10] | X | | | | | | | X | | | | | | X | | X |
| Optional blood sample for immune reconstitution and future research[11,13] | X | | X | | | X | | | | | X | | | X | | |
| Optional bone marrow aspirate for MRD assessment and future research[12,13] | X | | | | | | | | | | | | | X | | |

[1] Weekly laboratory monitoring (± 2 days) is required during Cycles 1 and 2. Laboratory monitoring is required once every cycle for all other cycles.
[2] See table 4.2.1d for target dates for these endpoint assessments.
[3] Blood chemistries include: bilirubin, alkaline phosphatase, AST and ALT.
[4] Estimated creatinine clearance is calculated using the Cockcroft-Gault formula and actual body weight.
[5] Bone Marrow aspirate and biopsy required only to confirm CR in patients.
[6] Assessment to be performed more frequently if clinically indicated.
[7] Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points and may be performed more frequently if clinically indicated.
[8] GVHD assessments will be done **weekly** from 7 days post-maintenance intiation until 60 days post-maintenance initiation; after 60 days they will be done **once every cycle**.
[9]The toxicity assessment will include a review of **all** toxicities and appropriate lab evaluations experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC.
[10] Health quality of life assessment, SF-36 and FACT-BMT, should be completed prior to Maintenance, after cycle 6 of maintenance, within 28 days of completing maintenance therapy, and at 2 years post-transplant (24T) for English- and Spanish-speaking patients only.
[11] Blood Samples for future research will be collected prior to randomization, at initiation of cycle 2 or approximately day 100 post transplant at cycle 5 or approximately day 180 post transplant, at cycle 10 or approximately 1 year post transplant and one month after completion of maintenance. Blood samples taken prior to maintenance, at Cycle 5, and after Cycle 12 will also be sent for immune reconstitution analysis at Roswell Park Cancer Institute. See Appendix C for procedures and Appendix L for details.
[12] Minimal residual assessment will be done in bone marrow aspirate centrally at Roswell Park Cancer Institute. See Appendix C for procedures and Appendix L for details.
[13] Optional blood and bone marrow samples must be collected ≤ 14 days prior to the initiation of maintenance therapy. The samples should be collected AFTER randomization and BEFORE initiation of maintenance therapy, however samples collected prior to randomization that fall within this window may be accepted.

## Table 4.3.3: Patient Clinical Assessments for Non-Randomized Patients (After 120 Days Post-Transplant)

| Study Assessments/Testing | Months Post Transplant | | | |
|---|---|---|---|---|
| | 6 | 12 | 18 | 24 |
| CBC, differential, platelet count, and blood chemistries[1] | X | X | X | X |
| Quantitative serum immunoglobulins | X | X | X | X |
| SPEP and immunofixation | X | X | X | X |
| 24 Hour Urine for UPEP, protein excretion and immunofixation | X | X | X | X |
| Serum free light chain ratio | X | X | X | X |
| Bone marrow aspirate and biopsy | X[5] | X[5] | X[5] | X[5] |
| Skeletal Survey[2] | | | X | X |
| Chronic and Acute GVHD assessment | X | X | | |
| Toxicity assessment[3] | X | X | X | X |
| Health-Related Quality of Life[4] | | | | X |
| Optional blood sample for future and immune reconstitution research | X | X | | |

[1] Blood chemistries include: bilirubin, alkaline phosphatase, AST and ALT.
[2] Assessment to be performed more frequently if clinically indicated.
[3] The toxicity assessment will include a review of **all** toxicities and appropriate lab evaluations experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC.
[4] Health quality of life assessment, SF-36 and FACT-BMT should be completed at 2 years post-transplant.
[5] Required only to confirm CR and as clinically indicated.

## 4.4. Data Reporting

### 4.4.1. Criteria for Forms Submission

Forms that are not entered into AdvantageEDC$^{SM}$ within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC$^{SM}$ and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File.

### 4.4.2. Reporting Patient Deaths

Recipient death information must be entered into AdvantageEDC$^{SM}$ within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC$^{SM}$.

### 4.4.3. Adverse Event Reporting

Reporting of adverse event on the BMT CTN 1302 trial has unique requirements due to the addition of bortezomib and ixazomib as part of the protocol. Adverse event reporting requirements are summarized below and further described in Appendix I.

#### 4.4.3.1. Definitions

**Adverse Event**: An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

**Expectedness**: An adverse event can be Expected or Unexpected

- **Expected adverse events** are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- **Unexpected adverse events** are those that vary in nature, intensity or frequency from information in the current adverse event list, the Investigator's Brochure, the package insert, or when it is not included in the informed consent document as a potential risk.

#### 4.4.3.2. BMT CTN Adverse Event Reporting Guidelines

It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment. Reporting of AEs for BMT CTN 1302 will be consistent with the BMT CTN Manual of Procedures. Additional requirements specific to this protocol are outlined below and in Appendix I.

In BMT CTN studies, expected adverse events are reported via the web-based electronic data capture system, AdvantageEDC. Events are captured on calendar-driven case report forms (e.g., Toxicity and Hematology/Chemistry) or event-driven case report forms (e.g., Relapse/Progression, Secondary Graft Failure, and Death). Additionally, any expected grade 4 event not collected on another form must be reported through the expedited AE reporting system via AdvantageEDC.

Unexpected, grades 3-5 AEs, irrespective of the attribution of the event to the study drug/ procedure/treatment, will be reported through the expedited AE reporting system via AdvantageEDC, and will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The BMT CTN 1302 protocol has two distinct interventions; transplant and maintenance therapy. Determination of expectedness for events occurring post-transplant and/or post-maintenance therapy will be at the discretion of the investigator as described in Appendix I, section I.3. **Unexpected, grades 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event.** The NHLBI Data and Safety Monitoring Board will receive summary reports of all adverse experiences at least twice yearly.

#### 4.4.3.3. Adverse Event Reporting Following Progression

If a patient meets the protocol defined definition of progression (see Chapter 3), Unexpected Grade 3-5 Adverse Events and events listed in Appendix I are no longer required to be reported on the Adverse Event Form once the patient is more than 30 days from their last dose of maintenance treatment. However, SPMs should continue to be reported within three business days of the knowledge of the event through the end of the study follow-up period.

#### 4.4.3.4. Additional Adverse Event Reporting Requirements with Respect to Bortezomib and Ixazomib/Placebo

Millennium Pharmaceuticals, Inc. (MPI) is supplying bortezomib and ixazomib for this study and a description of additional adverse event reporting requirements for this study is detailed in **Appendix I**. The additional adverse event reporting period for bortezomib begins at the time of bortezomib administration and continues for 30 days. Due to the blinding of maintenance, the additional adverse event reporting period for ixazomib applies for all participants who receive maintenance and begins with the first dose of maintenance and continues until 30 days after the last dose of maintenance (ixazomib or placebo). Along with the additional adverse event reporting requirements, any adverse event reported through the expedited AE reporting system will include the investigator's assessment of relationship to bortezomib and maintenance therapy (unrelated, unlikely, possible, probable, definite, or not applicable).

#### 4.4.3.5. Procedures for Reporting Exposure to Bortezomib and/or Ixazomib during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while receiving bortezomib and/or ixazomib/placebo for this study, she must inform the Investigator immediately and permanently discontinue study drug. The pregnancy, suspected pregnancy, or positive pregnancy test must be

reported within 24 hours of the Investigator's knowledge of the pregnancy. The event must be reported through the expedited AE reporting system via AdvantageEDC$^{SM}$.

The Investigator will follow the subject until completion of the pregnancy, and must report the outcome of the pregnancy and neonatal status as a follow-up to the original expedited AE report in AdvantageEDC.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the Investigator must also immediately report the pregnancy as detailed above. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

4.4.3.6. Reporting of Second Primary Malignancies (SPMs)

All second primary malignancies (SPM), excluding non-melanoma skin cancers, experienced by patients enrolled on the BMT CTN 1302 study must be reported within three business days of knowledge of the event using the Adverse Event forms (AE1-AE6) in AdvantageEDC. The Event Description of the Adverse Event forms should include histologic type. Reporting of SPMs in AdvantageEDC is required until all patients have completed 2 years of follow up.

4.4.3.7 Adverse Event Reporting Following an SPM

Adverse Event reporting following an SPM is dependent on the treatment received for the reported SPM.

- If a patient experiences an SPM resulting in permanent discontinuation of maintenance and initiation of non-protocol systemic therapy, Unexpected Grade 3-5 Adverse Events and events listed in Appendix I are no longer required to be reported on the Adverse Event Form once the patient is more than 30 days from their last dose of maintenance.
- If a patient experiences an SPM that does *not* result in permanent discontinuation of maintenance, Adverse Events will continue to be reported as per section 4.4.3 and Appendix I of the protocol.
- Requests to discontinue Adverse Event Reporting for events that do not meet the criteria above will be considered on a case by case basis.

4.4.4. CIBMTR Data Reporting

Centers participating in BMT CTN trials must register pre- and post transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR). Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment in BMT CTN 1302 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post- transplant Comprehensive Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

Reporting of all SPMs is also required on CIBMTR follow up forms for patients during their 2-year participation on BMT CTN 1302, the extended follow-up period (until all patients have completed 2 years of follow up), and beyond.

# CHAPTER 5

# 5. STATISTICAL CONSIDERATIONS

## 5.1. Study Design and Objectives

The study is designed as a Phase II, randomized, multicenter double-blind, placebo controlled prospective comparative study of ixazomib maintenance therapy versus a placebo following allogeneic HCT for high risk multiple myeloma. The premise is that ixazomib will increase progression-free survival in patients as compared to a placebo. Patients will be enrolled prior to initiation of the conditioning regimen. Patients who are eligible at 60-120 days post transplant will be randomized to maintenance therapy or placebo and evaluated for the primary comparison of progression-free survival. Patients who are transplanted but not randomized will be followed for secondary endpoints. The target sample size is 110 patients randomized. We assume that 20% of patients will fail to meet criteria for randomization and so plan to enroll 138 patients receiving HCT in order to achieve the targeted number of randomized patients. Note that the conditioning regimen was changed in Version 2.0 of the protocol. The target sample size of 110 randomized patients was retained and the primary analysis will contain data from all randomized patients independent of the conditioning regimen.

### 5.1.1. Accrual

It is estimated that three years of accrual will be necessary to enroll the targeted sample size.

### 5.1.2. Randomization

Randomization will occur prior to initiation of maintenance therapy (approximately 60-120 days post transplant). Subjects eligible to initiate maintenance therapy will be randomized at a ratio of 1:1 between the treatment arms using permuted blocks of random sizes. Randomization will be stratified on number of prior progressions (none versus one or more).

### 5.1.3. Primary Endpoint

The primary endpoint of this study is progression-free survival (PFS) post-randomization treated as a time to event endpoint. Subjects achieving randomization will be eligible for the primary comparison. Death from any cause, progression, or initiation of anti-myeloma therapy as defined in Chapter 3 will be considered events for this endpoint. Patients will be censored at 2-years post transplant.

### 5.1.4. Primary Hypothesis

The primary null hypothesis of the study is that there is no difference in time to PFS post-randomization among randomized subjects receiving Ixazomib vs. Placebo maintenance therapy.

$$H_o: \quad HR_{ixazomib \text{ VS } placebo \geq 1}$$
$$H_a: \quad HR_{ixazomib \text{ VS } placebo < 1}$$

## 5.2. Sample Size and Power Calculations

To estimate the baseline event rate and determine the sample size, we used data from the high risk stratum of BMT CTN 0102[45]. BMT CTN 0102 defined high risk patients using presence of del13q by standard karyotyping or beta-2 microglobulin ≥4mg/L; 28 patients were biologically assigned to an autologoustransplant followed by an HLA-matched sibling transplant(auto-allo). The post-allogeneic transplant results are shown in Table 5.2.1.

**Table 5.2.1: BMT CTN 0102: Patients With High Risk Myeloma Assigned to Auto-Allo Transplantation**

| 0102 high risk allo (n=28)* | All Patients PFS % | Alive and free of disease at day 100 PFS % (n=25) |
|---|---|---|
| 3 month | 89 | 100 |
| 6 month | 75 | 84 |
| 12 month | 61 | 68 |
| 18 month | 54 | 60 |
| 24 month | 50 | 56 |

*In this table, time points are post transplant

The target sample size is 110 patients randomized. It is anticipated that 10% of subjects will experience an event (death or progression) prior to randomization and another 10% will be otherwise ineligible for maintenance, therefore, in order to achieve 110 randomized patients, we anticipate enrolling 138 transplanted patients.

A piecewise-linear progression-free survival curve was assumed for randomized placebo subjects and fit to probabilities 85%, 70%, 60% and 55% at 3, 9, 15, and 21 months post-randomization (approximately 6, 12, 18, and 24 months post transplant). Table 5.2.2 shows the power to detect various hazard ratios for a one-sided log rank test with a type I error of 10%. The design assumes patients are randomized on approximately Day 90 and censored at 21 months post-randomization. Power calculations were performed using SAS version 9.3.

**Table 5.2.2: Probability of Rejecting the Null Hypothesis of Greater Than or Equal to Hazards in Placebo and Maintenance Arms**

| Hazard Ratio among Randomized Subjects Ixazomib vs Placebo | PFS Probability for Randomized Ixazomib Subjects at 21 Months Post-Randomization | Probability of Rejecting Null Hypothesis |
|---|---|---|
| 0.37 | 80.2% | 94.1% |
| 0.42 | 77.8% | 89.9% |
| 0.48 | 75.0% | 82.8% |
| 0.6 | 69.9% | 63.5% |
| 1.00 | 55.0% | 10% |

By randomizing post transplant, the observed difference between treatment arms is more pronounced than if randomization occurred prior to transplant. As a secondary analysis, PFS from transplant for each maintenance strategy will also be estimated as described in section 5.6.3. As the main objective of this trial is to assess whether maintenance is a promising approach for high risk patients undergoing allogeneic transplantation, the type I error and primary hypothesis are one-sided to allow detection of an effect size in line with expected benefits of maintenance therapy. This is not intended to be a definitive trial but instead provide possible evidence of a benefit while exposing a limited number of subjects to the potential risks of maintenance therapy.

## 5.3. Interim Analysis

There will be no formal interim analysis for futility or efficacy for this trial. We will prospectively monitor the percentage of patients not achieving randomization to ensure feasibility and to monitor the assumptions included in the sample size and power considerations. Centers with such patients not enrolled by Day 90 will be contacted. Furthermore, the test described below will serve as a trigger to identify if the rate of non-randomization exceeds what is expected.

Version 2.0 of the protocol changed the conditioning regimen by removing post-transplant bortezomib due to unanticipated early toxicities. Monitoring of the proportion of patients not achieving randomization will be restarted among patients transplanted with the new regimen. This approach allows the new transplant regimen to be monitored independently of the original regimen, as the new regimen is anticipated to have less toxicity and, thus, likely a higher proportion of patients achieving randomization.

The proportion of patients not achieving randomization by Day 120 will be monitored using a binomial Sequential Probability Ratio Test (SPRT). Monitoring for non-randomization will be performed monthly beginning after the third month of enrollment until four months after the last subject is transplanted. At least three events must be observed in order to trigger review. The binomial SPRT can be represented graphically. At each monthly interim analysis, the sufficient statistics are plotted against each other, with total number of patients on the y-axis and the total number of observed events on the x-axis. The continuation region of the test is defined by two parallel lines. Only the upper boundary will be used to protect against an excess proportion of non-randomized patients. If the graph rises above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more non-randomized patients than predicted by the total number of patients who have reached the evaluation time point. Otherwise, the SPRT continues until the last subject has reached the evaluation time point for that guideline.

A SPRT contrasting 20% versus 30% 120-day incidence of non-randomization results in decision boundaries with a common slope of 0.248 and an upper intercept of 3.63, with nominal type I and II errors of 12% and 15%, respectively.

The actual operating characteristics of this truncated test, shown in Table 5.3.1, were determined in a simulation study that assumed uniform accrual of 138 individuals over a three-year time period and the last monitoring occurred at month 40 (3 years plus 120 days).

**Table 5.3.1: Operating Characteristics of Sequential Testing Procedure From a Simulation Study With 100,000 Replications**

**Proportion of Eligible Patients Not Randomized at Day 120**

| **True 120-Day Rate** | **20%** | **23%** | **27%** | **30%** |
|---|---|---|---|---|
| Probability Reject Null | 0.09 | 0.26 | 0.63 | 0.84 |
| Mean Month Stopped | 38.2 | 34.9 | 27.6 | 21.8 |
| Mean # Not Randomized by Day 120 | 26.2 | 27.3 | 24.5 | 20.6 |
| Mean # Patients Enrolled | 131.0 | 118.5 | 90.8 | 68.9 |

The testing procedure for non-randomization rejects the null hypothesis in favor of the alternative 9% of the time when the true 120 day rate is 20%, and 84% of the time when the rate is 30%. This corresponds to a type I error rate of $\alpha = 0.09$ and a type II error rate of $\beta = 0.16$. On average, if the true rate of non-randomization is 30%, the DSMB will be consulted 22 months after the trial has opened, when 21 patients did not achieve randomization out of 69 patients enrolled.

## 5.4. Safety Stopping Guidelines

Monitoring of key safety endpoints, Treatment Related Mortality (TRM) and aGVHD will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review. The key safety endpoints to be monitored are the rate of TRM at Day 100 post-transplant in all transplanted subjects, Grades III-IV aGVHD at Day 100 post-transplant, and Grades III-IV aGVHD rates at Day 60 post-randomization within treatment arm. Monitoring TRM post- transplant in all subjects will guard against poor outcomes resulting from the use of allogeneic transplants in high risk multiple myeloma subjects and monitoring the rate of severe aGVHD will allow assessment of severe transplant toxicity. Monitoring aGVHD rates post-randomization within treatment arm will protect against unexpectedly high aGVHD as a result of the maintenance therapy. Monitoring within arm will allow the DSMB to potentially close a single treatment arm if poor outcomes are observed. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for monitoring, as described in greater detail below and in Appendix I.

### 5.4.1. TRM at Day 100 PostTransplant Stopping Guideline

The TRM stopping guideline below was restarted with the implementation of Version 2.0 of the protocol to allow the safety monitoring to be conditioning regimen-specific, i.e., the guideline below will focus on participants receiving the new conditioning regimen only. Note that due to the small number of randomized participants prior to Version 2.0 of the protocol, the sample size estimate for the stopping guideline was retained at 138, as that itself is an estimate based off an assumption of 20% transplanted, but not randomized.

This sequential testing procedure conserves type I error at 5% across all of the monthly examinations for a treatment arm. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints (e.g., patients experiencing death without relapse/progression). The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive 100-day TRM. If the graph crosses the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum.

This procedure assumes a censored exponential distribution for the time until TRM during the first 100 days, and censors follow-up time after 100 days. Only deaths that occur on or before the patient has been followed for 100 days are counted. Total time on study is computed as time from transplant to death, or to 100 days, whichever comes first, summed for all patients on study.

The usual measures of performance of an SPRT are the error probabilities $\alpha$ and $\beta$ of rejecting $H_0$ when $\theta = \theta_0$ and of accepting $H_1$ when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRT:

A SPRT contrasting 10% versus 25% 100-day TRM, which results in decision boundaries with a common slope of 0.66 and an upper intercept of 2.54, with nominal type I and II errors of 7% and 10%, respectively.

The actual operating characteristics of this truncated test, shown in Table 5.4.1, were determined in a simulation study that assumed uniform accrual of 138 individuals over a three-year time period with monitoring occurring monthly for 40 months

**Table 5.4.1: Operating Characteristics of Sequential Testing Procedure From a Simulation Study with 100,000 Replications**

**Treatment-Related Mortality at Day 100 POST-TRANSPLANT**

| **True 100-Day Rate** | **10%** | **15%** | **20%** | **25%** |
|---|---|---|---|---|
| Probability Reject Null | 0.04 | 0.35 | 0.83 | 0.98 |
| Mean Month Stopped | 39.7 | 31.9 | 18.7 | 10.7 |
| Mean # Endpoints in 100 Days | 13.3 | 16.2 | 12.8 | 8.8 |
| Mean # Patients Enrolled | 133.8 | 109.9 | 68.4 | 40.9 |

For example, the testing procedure rejects the null hypothesis in favor of the alternative 4% of the time when the true 100-day TRM incidence is 10%, and 98% of the time when the rate is 25%. This corresponds to a type I error rate of $\alpha = 0.04$ and a type II error rate of $\beta = 0.02$. When the true 100-day TRM incidence is 20%, on average, the DSMB will be consulted 19 months after opening, when 13 events have been observed in 68 patients.

### 5.4.2. Acute GVHD at Day 100 Post-Tranpslant Stopping Guideline

This monitoring guideline was added in Version 2.0 of the protocol. The purpose was to monitor for unanticipated severe aGVHD in the post-allogeneic transplant setting. Monitoring will be performed via the censored exponential SPRT. The hypothesis that post-randomization Day 100 Grade III-IV aGVHD ≤ 10% will be tested against the alternative that it is > 10% each month. The SPRT contrasting 10% versus 25% results in decision boundaries with a common slope of 0.66 and an upper intercept of 2.54, with nominal type I and II errors of 7% and 10%, respectively. The actual operating characteristics of this truncated test, shown in Table 5.4.2, were determined in a simulation study that assumed uniform accrual of 138 individuals over a three-year time period, with monitoring occurring monthly for 40 months

**TABLE 5.4.2: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 100,000 REPLICATIONS**

**ACUTE GVHD GRADE III-IV AT DAY 100 POST TRANSPLANT**

| **True 100-Day Rate** | **10%** | **15%** | **20%** | **25%** |
|---|---|---|---|---|
| Probability Reject Null | 0.04 | 0.24 | 0.83 | 0.99 |
| Mean Month* Stopped | 39.7 | 31.8 | 18.7 | 10.7 |
| Mean # Endpoints in 100 Days | 13.4 | 16.2 | 12.8 | 8.8 |
| Mean # Patients Randomized | 133.8 | 109.6 | 68.5 | 40.8 |

*Time from Transplant

For example, the testing procedure rejects the null hypothesis in favor of the alternative 4% of the time when the true 100-day Grade III-IV aGVHD rate is 10%, and 83% of the time when the rate is 20%. When the true Grade III-IV aGVHD rate is 20%, on average, the DSMB will be consulted 19 months after transplantation begins, when 13 events have been observed in 69 patients.

### 5.4.3. Acute GVHD at Day 60 Post-Randomization Stopping Guideline

This monitoring guideline was modified in protocol Version 2.0 to shorten the assessment timeframe from 100 days to 60d days. The guideline will focus on all randomized patients independent of transplant regimen.

A similar procedure will be applied to monitor for aGVHD Grades III-IV. The hypothesis that post-randomization Day 60 Grade III-IV aGVHD ≤ 8% will be tested against the alternative that it is > 8% each month. The SPRT contrasting 8% versus 23% results in decision boundaries with a common slope of 0.95 and an upper intercept of 2.24, with nominal type I and II errors of 7% and 10%, respectively.

The actual operating characteristics of this truncated test, shown in Table 5.4.2, were determined in a simulation study that assumed uniform accrual of 55 individuals per arm over a three-year time period with monitoring occurring monthly for 38 months

**Table 5.4.2: Operating Characteristics of Sequential Testing Procedure From a Simulation Study with 100,000 Replications**

**Acute GVHD Grade III-IV at Day 100**

| **True 60-Day Rate** | **8%** | **13%** | **18%** | **23%** |
|---|---|---|---|---|
| Probability Reject Null | 0.04 | 0.27 | 0.63 | 0.88 |
| Mean Month* Stopped | 37.0 | 32.6 | 25.0 | 17.8 |
| Mean # Endpoints in 60 Days | 4.3 | 6.1 | 6.6 | 6.0 |
| Mean # Patients Randomized | 53.6 | 47.6 | 37.3 | 27.1 |

*Time from Randomization

For example, the testing procedure rejects the null hypothesis in favor of the alternative 4% of the time when the true 60-day Grade III-IV aGVHD rate is 8%, and 88% of the time when the rate is 23%. This corresponds to a type I error rate of $\alpha = 0.04$ and a type II error rate of $\beta = 0.12$. When the true Grade III-IV aGVHD rate is 18%, on average, the DSMB will be consulted 26 months after randomization begins, when 7 events have been observed in 37 patients. In the event that randomization is closed due to excess toxicity on one of the treatment arms, the alternate arm would remain open due to the importance of the secondary analysis as described in Section 5.6.3.2

## 5.5. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, Karnofsky/Lansky performance status, prior HCT, number of prior progressions, disease risk characteristics, disease response, donor type, time from transplant to initiation of maintenance therapy, and transplant regimen. Between groups comparisons will be performed for continuous variables via a non-parametric test and for categorical variables, via the chi-square test.

## 5.6. Analysis Plan

### 5.6.1. Analysis of the Primary Endpoint

The primary outcome of the trial is progression-free survival post-randomization. Progression or initiation of anti-myeloma therapy (as defined in Chapter 3) and death from any cause will be considered as events. The primary analysis will be performed using a one-sided log-rank test with a type I error of 10% among patients randomized to either maintenance or placebo. Patients will be censored at 2-years post transplant. Due to the dual questions being addressed by this *blinded* study (effects of allogeneic transplant and effects of maintenance therapy post-allogeneic transplant), the primary analysis will be completed after all randomized subjects have been followed for two years post transplant allowing both questions to be addressed *without risking premature unblinding*. Note that while the transplant regimen was modified in Version 2.0 of the protocol, the primary analysis will include all randomized patients. A secondary sensitivity analysis will look at randomized patients stratified by transplant regimen, but is not powered to detect regimen effect.

### 5.6.2. Analysis of Secondary Endpoints

#### 5.6.2.1. Acute GVHD of grades III-IV

Cumulative incidence of acute GVHD grades III-IV from randomization will be estimated using the cumulative incidence function, treating death prior to aGVHD as the competing risk. Cumulative incidence of aGVHD from randomization will be compared between treatment arms using Gray's test.

#### 5.6.2.2. Chronic GVHD (cGVHD)

Cumulative incidence of cGVHD from randomization will be estimated using the cumulative incidence function, treating death prior to cGVHD as the competing risk. Cumulative incidence of cGVHD from randomization will be compared between treatment arms using Gray's test.

#### 5.6.2.3. Response to treatment

Best response (sCR, CR, VGPR, or PR) after randomization will be compared between treatment groups using a chi-square test. Additionally, responses at 12 months and 18 months post-randomization will be assessed in each arm. These will be summarized separately for patients in CR at the time of randomization vs. those who were in less than a CR. Finally, best response at Day 60 (prior to randomization) will be reported for all transplanted patients.

#### 5.6.2.4. Progression

Cumulative incidence of progression from randomization will be estimated using the cumulative incidence function, treating death in remission as a competing risk. Cumulative incidence of progression from randomization will be compared between the treatment arms using Gray's test.

#### 5.6.2.5. Overall survival

Overall survival (OS) from randomization will be estimated for each treatment group using the Kaplan-Meier estimator and compared between the groups using the log-rank test.

#### 5.6.2.6. Treatment-related mortality

The event is death occurring from causes other than progression. Cumulative incidence of treatment-related mortality (TRM) from randomization will be estimated using cumulative incidence function, treating progression as a competing risk. Cumulative incidence of TRM from randomization will be compared between the treatment arms using Gray's test.

#### 5.6.2.7. Incidence of toxicities grade ≥ 3

All Grade ≥ 3 toxicities will be tabulated by grade for each treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as

well as cumulative over time. The cumulative incidence of Grade ≥ 3 toxicity will be compared between treatment arms at 6, 12 and 18 months post randomization.

5.6.2.8. Incidence of infections

The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity, and time period after randomization. The cumulative incidence of severe, life-threatening, or fatal infections, treating death as a competing event, will be compared between the two treatment arms at 6, 12 and 18 months post randomization.

5.6.2.9. Health Quality of Life

Health quality of life will be described from time of pre transplant to time prior to randomization utilizing the FACT-BMT self report, transplant specific questionnaire and the generic quality of life tool, the SF-36. Comparisons between maintenance treatment groups will be performed prior to maintenance, 6 months after start of maintenance and at 24 months after transplant. Only English and Spanish speaking patients are eligible to participate in the HQL component of this trial

5.6.2.10. Rate of Non-Randomization

The proportion of patients not achieving randomization by Day 120 post allogeneic HCT will be reported. Reasons for not initiating maintenance will be described.

5.6.3. Secondary Analysis – Time from Transplant

The following secondary analyses focus on time from transplant and analysis in the event of a study arm closure. Note that with the change to the transplant regimen in Version 2.0, the following analyses will be modified to look at an effect within each maintenance strategy and estimate a regimen-specific effect within each maintenance strategy, although the study is not specifically powered to look at a regimen difference.

5.6.3.1. Treatment Policy Estimation

While time from randomization is used for the primary analysis, estimates of the primary and key secondary endpoints from time of transplant are also clinically relevant. A secondary analysis will estimate PFS and overall survival for each maintenance strategy using the inverse weighted estimators of Lunceford et al[132]. Similarly, cumulative incidence of aGVHD grade III-IV, chronic GVHD, progression, and TRM from transplant will be estimated for each maintenance strategy using the inverse weighted estimator of Yavuz[133].

This analysis is similar to that of a dynamic or adaptive treatment trial (please note this does not refer to an adaptive design) where responders to an upfront treatment are randomized after a period on trial to a second treatment. Here the response is eligibility for initiation of maintenance and there is only one upfront treatment (allogeneic transplant). This provides two possible treatment regimens: 1) allogeneic transplant followed by ixazomib for subjects able and willing to tolerate

maintenance and standard of care for all other subjects and 2) allogeneic treatment followed by no maintenance for eligible subjects and standard of care for other subjects. Note that under the second strategy all subjects receive standard of care. For this trial, three distinct groups of subjects exist: 1) subjects randomized to ixazomib, 2) subjects randomized to no maintenance (i.e. placebo) and 3) subjects not able or willing to be randomized. Weights are based on response and the inverse probability of being assigned to a treatment strategy. To estimate outcomes for the first treatment strategy (allogeneic transplant followed by ixazomib if possible), subjects randomized to ixazomib will receive a weight of 2, subjects not achieving randomization will receive a weight of 1, and subjects randomized to no maintenance will receive a weight of zero. Thus, the ixazomib treatment strategy is estimated based on a mixture of outcomes from subjects receiving ixazomib (who represent another similar subject who could have been randomized to ixazomib but was not) and those not achieving randomization. A similar weighted approach will be used for the allogeneic transplant followed by no maintenance treatment strategy.

5.6.3.2. Analysis in the Event of Study Arm Closure.

In addition to pre-specified monitoring guidelines for acute GVHD Grades II-IV. The DSMB periodically reviews interim data to ensure patient safety. If a decision is made to close a study arm due to excess or unanticipated toxicities (i.e. death, progression, GVHD, etc) there is clinical interest in continuing accrual to the alternative arm as the impact of allogeneic transplant in this patient population is not well established.

For analysis purposes, continuing accrual when randomization has been closed will create four distinct groups of subjects: 1) Randomized to ixazomib, 2) Randomized to placebo, 3) Not Randomized, 4) Enrolled after randomization is closed. The weights from Lunceford et al are based on response, the probability of being randomized to one treatment or the other, and randomized treatment assignment. Non-randomized subjects are spread equally across treatment arms. As the probability of randomization is 0.5, a subject randomized to a maintenance strategy receives a weight of 2 compared to non-responders (weight of 1) and patients randomized to the alternate strategy (weight of 0).

Consider the scenario where the ixazomib arm is closed and subjects continue to accrue to the placebo arm (a similar situation would apply if the placebo arm is closed). The weight for subject i is given by: $Q_i = 1 - R_i + \pi^{-1} R_i Z_i$ where Ri is a binary indicator for response, $\pi$ is the randomization probability and Zi is a binary indicator of 0 for ixazomib and 1 for placebo.

To estimate outcomes for allogeneic transplant followed by no maintenance, Group 1 subjects (Ri=1, Zi=0, $\pi$=0.5) would receive a weight of zero as their treatment was inconsistent with this strategy ($Q_i = 1 - 1 + 0.5^{-1} * 1 * 0 = 0$). Group 2 subjects (Ri=1, Zi=1, $\pi$=0.5) would receive a weight of 2 ($Q_i = 1 - 1 + 0.5^{-1} * 1 * 1 = 2$) as their treatment was consistent, they responded and were randomized. Group 3 subjects (Ri=0 and Zi unknown) would receive a weight of 1 ($Q_i = 1 - 0 + \pi^{-1} * 0 * Z_i = 1$) as they did not respond. Finally Group 4 subjects could be broken down into non-responders ((Ri=0) and responders (Ri=1, Zi=1, $\pi$=1). Note that the randomization probability is now 1 as both the randomization is closed and as a result all group 4 subjects would

receive a weight of 1 ($Q_i = 1 - 0 + \pi^{-1} * 0 * Z_i = 1$ for non-responders and $Q_i = 1 - 1 + 1^{-1} * 1 * 1 = 1$ for responders).

As the primary hypothesis can no longer be feasibly tested the secondary analysis could still be powered based on a desired confidence interval width for PFS 2 years post-allogeneic transplant. The original sample size was 138 transplanted subjects with 110 randomized. Table 5.6.1 shows confidence interval widths based on a binomial proportion for a variety of sample sizes. The Kaplan-Meier estimate reduces to the binomial proportion in the absence of censoring and minimal censoring is anticipated given the short follow-up (2 years) and hard endpoint of progression or death.

**Table 5.6.1: 95% Confidence Interval Width for 2 Year Progression Free Survival Assuming a Probability of 0.5 and Minimal Censoring**

| Number Transplanted | Asymptotic | | | Continuity Correction | | |
|---|---|---|---|---|---|---|
| | Width | Lower | Upper | Width | Lower | Upper |
| 60 | 0.25 | 0.37 | 0.63 | 0.27 | 0.37 | 0.64 |
| 70 | 0.23 | 0.38 | 0.62 | 0.25 | 0.38 | 0.62 |
| 80 | 0.22 | 0.39 | 0.61 | 0.23 | 0.38 | 0.62 |
| 90 | 0.21 | 0.40 | 0.60 | 0.22 | 0.39 | 0.61 |
| 100 | 0.20 | 0.40 | 0.60 | 0.21 | 0.40 | 0.60 |
| 110 | 0.19 | 0.41 | 0.59 | 0.20 | 0.40 | 0.60 |
| 120 | 0.18 | 0.41 | 0.59 | 0.19 | 0.41 | 0.59 |
| 138 | 0.17 | 0.42 | 0.58 | 0.17 | 0.41 | 0.59 |

Note Table 5.6.1 is based on the variance for a binomial proportion of progression-free survival probability of 50% at 2 years based on the BMT CTN 0102 data. Actual width of the confidence interval may vary depending on the censoring pattern and number of patients in each of the groups.

# APPENDIX A
# PLASMA CELL LEUKEMIA RESPONSE CRITERIA

# APPENDIX A

## PLASMA CELL LEUKEMIA RESPONSE CRITERIA

**Stringent Complete Response (sCR):**
sCR required in addition to CR (defined below), all of the following:

- Absence of malignant plasma cells in the bone marrow by flow cytometry
- Absence of malignant plasma cells in peripheral blood by flow cytometry
- Normal free light chain ratio (FLC)

**Complete Response (CR)**
CR requires *all* of the following:

- Less than 5% plasma cells in a bone marrow aspirate
- Absence of plasma cells in peripheral blood
- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation[1].
- Absence of extramedullary disease

**Very Good Partial Response (VGPR)**
VGPR requires *all* of the following:

- Less than 5% plasma cells in a bone marrow aspirate
- Absence of plasma cells in the peripheral blood
- Greater than or equal to 90% reduction of serum monoclonal paraprotein plus paraprotein <100 mg/24hrs[2]
- Absence of extramedullary disease

**Partial Response (PR)**
Partial response requires *all* of the following:

- Between 5% and 25% plasma cells in a bone marrow aspirate
- Between 1% and 5% plasma cells in the peripheral blood
- Greater than or equal to 50% reduction of serum monoclonal paraprotein and reduction in 24- hour urinary monoclonal paraprotein by greater than or equal to 90% plus less than 200 mg/24hr[3]

[1] If the serum and urine M-Protein are unmeasurable, a normal serum kappa/lambda FLC ratio is also required.
[2] If the serum and urine M-Protein are unmeasurable, a greater than or equal to 90% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-Protein.
[3] If the serum and urine M-Protein are unmeasurable, a great than or equal to 50% decrease in the difference between involved and uninvolved FLC levels is required instead of the M-Protein.

- Greater than or equal to 50% reduction in the size of extramedullary disease

**Stable Disease (SD)**

- Patients who do not meet the criteria for sCR, Cr, VGPR, PR or progressive disease (defined below) are considered to have stable disease (SD)

**Progressive Disease (PD)**
Progressive disease requires on or more of the following.

- Greater than 25% increase in the plasma cells in a bone marrow aspirate, or an absolute increase of greater than or equal to 10%
- Greater than 5% absolute increase in plasma cells in the peripheral blood
- Greater than 25% increase in the level of the serum monoclonal paraprotein with an absolute increase of greater than or equal to 5 g/L
- Greater than 25% increase in the 24-hour urine protein electrophoresis with an absolute increase of at least 200 mg/24 hours
- Hypercalcemia
- Definite increase in lytic bone lesions
- Definite increase in the size or number of extramedullary disease.

# APPENDIX B
# PATIENT INFORMED CONSENT FORM

**Informed Consent to Participate in Research**



**Your Name:** _____

**Study Title:** Multicenter Phase II, Double-Blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Stem Cell Transplantation for High Risk Multiple Myeloma

**Protocol:** BMT CTN 1302

**Principal Investigator:** *Insert local PI information*

**Sponsor:** The National Institutes of Health (NIH) is sponsoring this study by providing financial support for the coordination of this study through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

# 1. Introduction

We invite you to join this clinical trial, also known as a research study. You are being asked to join because:

- You are at least 18 and no older than 70 years of age.
- You have high risk **multiple myeloma (MM)**, a cancer of the plasma cells that begins in your bone marrow, OR your MM returned after an **autologous transplant.**
- You have a closely matched related or unrelated peripheral blood stem cell donor.

Because there's no cure for MM, **maintenance treatment (chemotherapy)** is given to slow the return of your disease after an **allogeneic transplant**. We are doing this study to learn if maintenance treatment (chemotherapy) works better to control your disease than placebo (pill that doesn't have any active maintenance drugs).

For this study, the type of allogeneic transplant you will get is called a **peripheral blood stem cell (PBSC) transplant**. Your doctor also wants to use a **reduced-intensity or non-myeloablative conditioning regimen** for your transplant.

This study will take at least 3 years and will include 138 participants. Your participation will last **2 years**. After that time, selected additional data will be collected until all patients on the study have been followed for 2 years.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.
- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.

- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

## 2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

For this study, you will receive a type of allogeneic transplant called peripheral blood stem cell (PBSC) transplant. Allogeneic transplant is a common treatment for patients with high risk MM. Having high risk MM means that:

- Your doctor found abnormal cells when he or she looked at the genetics of your bone marrow cells, OR
- Your disease came back (relapsed) less than 24 months after an autologous transplant, OR
- You have a fast growing type of myeloma called plasma cell leukemia.

An allogeneic transplant uses blood-making cells from a family member or an unrelated donor to remove and replace your abnormal blood cells. With a PBSC transplant, the donor cells come from his or her blood stream.

Your doctor also wants to use a reduced-intensity or non-myeloablative conditioning regimen for your transplant. The conditioning regimen is the chemotherapy used to destroy the diseased cells before you get your donor cells. A reduced-intensity or non-myeloablative conditioning regimen uses lower doses of chemotherapy.

There's no cure for MM. After transplant, the disease will almost always return, or relapse. Some patients may keep getting treatment after transplant called maintenance treatment. Maintenance treatment is given to slow down relapse.

## 3. Study Purpose

We are inviting you to take part in this study because you have cancer of the plasma cells, your disease is high risk or relapsed after autologous transplant, and an allogeneic transplant is a treatment option for you. We are doing this study to learn more about ways to prevent or delay relapse of multiple myeloma (MM).

We will use 2 treatments to see which one is better at preventing or delaying relapse of MM (**Table 1**).

This study will help doctors make the best choice about treatment after allogeneic transplant for patients with MM.

**Table 1. Study Treatment Groups**

| **Treatment Group A (allogeneic transplant and experimental maintenance treatment)** | **Treatment Group B (allogeneic transplant and no maintenance treatment)** |
|---|---|
| ▪ Fludarabine<br>▪ Melphalan<br>▪ Bortezomib<br>▪ Allogeneic peripheral blood stem cell transplant<br>▪ Tacrolimus<br>▪ Methotrexate<br>▪ Ixazomib (experimental maintenance pill) | ▪ Fludarabine<br>▪ Melphalan<br>▪ Bortezomib<br>▪ Allogeneic peripheral blood stem cell transplant<br>▪ Tacrolimus<br>▪ Methotrexate<br>▪ Placebo (no maintenance) |

## 4. Rights to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

## 5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for 2 years after your transplant. After that time, selected additional data will be collected until all patients on the study have been followed for 2 years.

**Before You Start Your Treatment**

You will need to have several check-ups and tests to see if you can be in the study. All patients participating in this study need to have a matched donor. These check-ups and tests are part of your regular cancer and transplant care. You may need to have them even if you do not join the study. See **Table 2. Timeline of Tests for Your Transplant** for a schedule of when we will give you the physical tests.

**During Your Treatment**

Conditioning Regimen Before Transplant

The conditioning regimen is the chemotherapy you will receive before you get your donor cells. This helps the donor cells start to grow and make new cells in your bone marrow (engraft). It also helps to kill cancer cells. The regimen includes fludarabine, melphalan, and bortezomib, given by intravenous infusion (IV) in your arm. How often you will get these drugs is shown in **Table 3**.

1. Six days before your transplant, we will start giving you fludarabine, which you will get for 4 days.
2. Then, 4 days before your transplant, we will give you melphalan, which you will get for 2 days.
3. We will give you bortezomib once 3 days before your transplant.

You will have check-ups during the conditioning regimen to see how well your organs are working. If your organs are not working properly, your doctor will lower the dose of the chemotherapy drugs.

- **Infusion of Peripheral Blood Stem Cells (Transplant)**

On your transplant day (Day 0), the donor cells (stem cells) will be given to you through your catheter, like a blood transfusion. The cells will travel to your bone marrow where they will start to make healthy, new blood cells.

**Table 2. Timeline of Tests for Your Transplant**

| **Tests** | **Weeks Before/After Transplant** | | | | | | | | | | **Days After Transplant** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -2 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 100 | 120 |
| Medical history | X | | | | | | | | | | | |
| Blood tests for cell counts, liver and kidney function | X | X | X | X | X | X | X | X | X | X | X | X |
| Heart and lung function tests | X | | | | | | | | | | | |
| Pregnancy test | X | | | | | | | | | | | |
| Tests to see how much cancer you have | X | | | | | | | | X | | | X |
| Bone marrow tests | X | | | | | | | | X | | | X |
| Optional blood sample for future research (if you consent) | X | | | | X | | | | | | X | |
| Optional bone marrow sample for research (if you consent) | X | | | | | | | | | | | |
| Tests to see how many donor cells you have | | | | | | | | | X | | | |
| Tests for GVHD | | X | X | X | X | X | X | X | X | X[2] | | X |
| Questionnaire about your Quality of Life[1] | X | | | | | | | | | | | |

[1]English- and Spanish-speaking patients only.
[2]Tests for GVHD will continue weekly until 14 weeks after transplant

**Table 3: Timeline of Transplant and GVHD Drugs**

| Drug | Treatment Day | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -6 | -5 | -4 | -3 | -2 | -1 | 0* | +1 | +3 | +4 | +6 | +7 | +8 | +11 |
| Fludarabine | X | X | X | X | | | | | | | | | | |
| Melphalan | | | X | X | | | | | | | | | | |
| Bortezomib | | | | X | | | | | | | | | | |
| PBSC infusion | | | | | | | X | | | | | | | |
| Tacrolimus | | Tacrolimus will be given on a timeline that is determined by the institution's guidelines | | | | | | | | | | | | |
| Methotrexate | | | | | | | | X | X | | X | | | X |

*Day 0 = day of transplant

- **GVHD Prevention Drugs**

You will be given drugs (tacrolimus and methotrexate) to prevent **graft-versus-host disease (GVHD)**. GVHD is a common side effect of allogeneic transplant. It's a medical condition that can become very serious. GVHD happens because of differences between your own immune cells (host) and the immune cells from your donor (graft). Your new immune system, or the donated cells, might see your cells as foreign and attack them.

GVHD can cause:

- Skin rashes
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Liver damage
- Hepatitis or jaundice
- Increased risk of infection

We will give you tacrolimus by pill or IV beginning 3 days before your transplant. We will give you less and less until we stop it completely. This can take several months.

After Your Transplant

To prevent GVHD, we will also give you methotrexate by IV on Days 1, 3, 6, and 11 after your transplant (**Table 3**).

We will test (evaluate) your health during the study. You will be watched closely for any signs and symptoms of GVHD. See **Table 2. Timeline of Tests for Your Transplant** for a schedule of when we will give you the physical tests.

Before Your Maintenance Treatment

At least 14 days before you start maintenance therapy, we will check to make sure you are healthy enough to start maintenance treatment. See **Table 4. Timeline of Tests for Your Maintenance Treatment** for a schedule of when we will give you the physical tests. If you are not healthy enough to start maintenance therapy, you will continue to be followed on this study until two years after your transplant regardless of what treatment you receive.

Randomization

We will use a computer program to assign you by chance to treatment group A or B. You won't be able to choose your group. Once you are assigned to a group, you can't change to the other group. The study doctor can't change your group either. You will have an equal chance of being placed in either group.

During Your Maintenance Treatment

- **Treatment Group A: Ixazomib**

If you are assigned to Treatment Group A, we will give you ixazomib as a pill on Days 1, 8, and 15 of each cycle (28 days in each cycle). This means that you will take ixazomib once a week for 3 weeks, and then have 1 week off. We will repeat the cycle 12 times or for about 1 year.

- **Treatment Group B: Placebo**

If you are assigned to Treatment Group B, we will give you the placebo as a pill (sugar pill). The placebo pills will look exactly like ixazomib, but don't have any drugs or treatment. We will give you the placebo pill on Days 1, 8, and 15 of each cycle (28 days in each cycle). This means that you will take the placebo once a week for 3 weeks, and then have 1 week off. We will repeat the cycle 12 times or for about 1 year.

- **Maintenance Treatment Dose (Treatment Group A and B)**

It's important that you take the pill at the same time with each dose. Also, you will have to keep a record of the pills you take. This means that you will write down what day and time you take every pill.

We will watch your health closely during maintenance treatment, including how well your organs work (function). We will raise your dose for Cycle 4 if your organs handle the treatment well. We will lower your dose if your organs don't handle the treatment well.

We won't start a new Cycle until your organ function returns to normal. If we lower your dose and then your organ function returns to normal, we won't raise your dose again.

We will stop the maintenance treatment if:

- Your disease progresses
- You have a serious side effect, like severe diarrhea or skin rash
- You have low blood cell counts
- You have serious GVHD
- You are a woman and become pregnant, or there is a chance that you are pregnant
- You go more than 56 days before starting a new maintenance treatment cycle
- You are unable to complete 12 cycles of maintenance treatment within 18 months of starting therapy
- You don't follow the study directions, or
- You choose to leave the study.

We will watch your health closely, especially if we change your treatment dose. You will need to have several check-ups and tests during your maintenance treatment. These tests are shown in **Table 4. Timeline of Tests for Your Maintenance Treatment.**

**Table 4. Timeline of Tests for Your Maintenance Treatment**

| **Tests** | **Cycle (28 days in each cycle)** | | | | | | | | | | | | | | **Month[1]** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Follow Up | 18 | 24 |
| Tests for toxicities, and infections | X | X | X | X | X | | X | | | X | | | X | X | X | X |
| Tests for GVHD | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Blood tests for cell counts, liver and kidney function | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tests to see how many donor cells you have | X | | | | | | X | | | | | | X | | | |
| Tests to see how much cancer you still have | X | | | X | | | X | | | X | | | X | | X | X |
| Tests to see how well your immune system is recovering | X | | | X | | | X | | | X | | | X | X | X | X |
| Bone marrow tests | X | | | X | | | X | | | X | | | X | X | X | X |
| Pregnancy blood test | X | | | | | | | | | | | | | | | |
| Optional blood samples for research (if you consent) | X | | X | | | X | | | | | X | | | X | | |
| Optional bone marrow samples for research (if you consent) | X | | | | | | | | | | | | | X | | |
| Questionnaire about your Quality of Life[2] | X | | | | | X | | | | | | | | X | | X |

[1]After 24 months of follow up, patients will continue to be monitored for the development of new cancers. This follow up period will end when all patients have been followed for 2 years.
[2] English- and Spanish-speaking patients only.

# 6. Risks and Discomforts

You may have side effects while on the study. Side effects can range from mild to serious. The risks and discomforts of peripheral blood stem cell transplant are the same if you join this study, or if you don't join this study.

You might do better or worse with a standard transplant. Your healthcare team may give you medicines to help with side effects like nausea (feeling sick to your stomach). In some cases, side effects can last a long time or may never go away.

**Risks of Medications**

The risks of the chemotherapy drugs, and or radiation you get as part of the treatment are listed below. How often patients get each of the side effects are shown in **Table 5**. **Risks and Side Effects**.

All immune suppressive drugs, except for bortezomib and ixazomib, are commonly used in allogeneic transplant.

**Table 5. Risks and Side Effects**

| | |
|---|---|
| **Likely** | What it means: This type of side effect is expected in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect. |
| **Less Likely** | What it means: This type of side effect is expected in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect. |
| **Rare, but Serious** | What it means: This type of side effect is expected in fewer than 2% of patients. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect. It doesn't happen very often, but is serious when it does. |

**Melphalan**

| **Likely**<br><br>(May happen in more than 20% of patients) | **Less Likely**<br><br>(May happen in less than 20% of patients) | **Rare, but Serious**<br><br>(May happen in less than 2% of patients) |
|---|---|---|
| ▪ Loss of appetite<br>▪ Constipation<br>▪ Diarrhea<br>▪ Nausea (feeling sick to your stomach) and vomiting (throwing up)<br>▪ Temporary hair loss<br>▪ Sensitive skin<br>▪ Infection<br>▪ Low number of white blood cells<br>▪ Low number of platelets in the blood with increased risk of bleeding<br>▪ Anemia (low number of red blood cells)<br>▪ Mouth sores<br>▪ Sore throat (red with swelling)<br>▪ Skin breakdown (if drug leaks from vein) | ▪ Changes in heart beat that cause you to dizzy, faint and short of breath<br>▪ Hepatitis (swelling of the liver)<br>▪ Kidney failure<br>▪ Weight loss<br>▪ Feeling weak | ▪ Allergic reaction<br>▪ Lung infection<br>▪ Scarring of lung tissue<br>▪ Seizure<br>▪ Vasculitis (inflammation of blood vessels)<br>▪ Low blood pressure<br>▪ Excessive perspiration<br>▪ Sterility (unable to have children)<br>▪ Liver damage<br>▪ Heart stops beating<br>▪ Cancer of bone marrow cells |

**Bortezomib (Velcade®)**

| **Likely**<br><br>(May happen in more than 10% of patients) | **Less Likely**<br><br>(May happen in less than 10% of patients) | **Rare, but Serious**<br><br>(May happen in less than 1% of patients) |
|---|---|---|
| ▪ Anemia (low number of red blood cells)<br>▪ Low number of platelets in the blood with increased risk of bleeding<br>▪ Feeling weak and uncomfortable<br>▪ Feeling tired<br>▪ Fever, with shaking chills<br>▪ Weight loss because not feeling hungry<br>▪ Constipation<br>▪ Diarrhea<br>▪ Nausea and vomiting<br>▪ Upset stomach or pain in the belly<br>▪ Pain, numbness and tingling in hands and feet<br>• Lowered white blood cells called neutrophils that may increase your | ▪ Low number of white blood cells<br>▪ Low blood pressure<br>▪ Changes in heart beat and feeling dizzy, faint and short of breath<br>• Heartburn, acid reflux and stomach bloating<br>▪ Bleeding in stomach or lungs<br>▪ Blood in urine<br>▪ Fluid build-up around the lungs<br>▪ Confusion<br>▪ Mouth or throat sores<br>▪ Changes in the way things taste<br>▪ Abnormal liver tests<br>▪ Blurred vision<br>▪ Redness and swelling in the eye<br>▪ Nose bleeds | ▪ Coughing up blood<br>▪ Reversible posterior leukoencephalopathy syndrome [RPLS]/Posterior reversible encephalopathy syndrome [PRES] (headache, confusion, seizures, and vision loss caused by very high blood pressure that comes on quickly)<br>▪ Hepatitis (swelling of the liver) and liver failure<br>▪ Pancreatitis (swelling of the intestines, stomach, or pancreas)<br>▪ Swelling and fluid build-up in and around the lungs or heart<br>▪ Hearing loss<br>▪ Bleeding in the brain<br>▪ Loss of some or all vision in one or both eyes |

| **Likely**<br><br>(May happen in more than 10% of patients) | **Less Likely**<br><br>(May happen in less than 10% of patients) | **Rare, but Serious**<br><br>(May happen in less than 1% of patients) |
|---|---|---|
| risk of infection and is uncommonly associated with fever; commonly you may have lowered white blood cells called lymphocytes or have lowered red blood cells, white blood cells and platelets at the same time.<br>▪ Skin rash with itching and redness<br>▪ Insomnia (trouble sleeping)<br>▪ Anxiety (feeling worried and nervous)<br>▪ Aches, pain and weakness in arm and leg muscles, joints and bones<br>▪ Cough<br>▪ Headache<br>▪ Flu-like symptoms such as chills, sore throat, and runny nose<br>▪ Edema (swelling in the arms and legs with weight gain) | ▪ Changes in blood sugar<br>▪ Changes in levels of sodium, calcium and potassium in the blood<br>▪ New or worse heart failure<br>▪ Infections of the bladder, sinuses, mouth, throat, stomach, intestines and skin<br>▪ Infections in the blood that can lead to death<br>• Kidney function that gets worse<br>• Fungal infections in the mucous membrane such as the mouth and throat and uncommonly in the skin and nails<br>• Muscular weakness | ▪ Encephalopathy (brain disorder that can lead to death)<br>▪ Sore mouth and throat<br>▪ Allergic reactions (swelling, of the skin, face or throat) that can lead to death<br>▪ Blistering rash with skin peeling and mouth sores that can lead to death<br>▪ Pain, swelling and red skin where bortezomib is injected<br>▪ Intestinal blockage<br>▪ Fast death of cancer cells that can hurt organs like the kidneys<br>▪ Severe muscle weakness and paralysis |

| **Likely**<br><br>(May happen in more than 10% of patients) | **Less Likely**<br><br>(May happen in less than 10% of patients) | **Rare, but Serious**<br><br>(May happen in less than 1% of patients) |
|---|---|---|
| • Herpes virus such as shingles (herpes zoster) that can sometimes cause local pain that does not go away for a while and herpes simplex virus. Shingles can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon<br>• Hair loss | | |

**Fludarabine**

| **Likely**<br><br>**(May happen in more than 20% of patients)** | **Less Likely**<br><br>**(May happen in less than 20% of patients)** | **Rare, but Serious**<br><br>**(May happen in less than 2% of patients)** |
|---|---|---|
| ▪ Mouth sores<br>▪ Nausea and vomiting<br>▪ Diarrhea<br>▪ Low number of white blood cells<br>▪ Low number of platelets in the blood | ▪ Pain, numbness and tingling in the hands and feet<br>▪ Feeling sleepy<br>▪ Weakness<br>▪ Changes in heartbeat<br>▪ Loss of appetite | ▪ Coma<br>▪ Inflammation of the lungs<br>▪ Cough<br>▪ Interstitial pneumonia (type of lung disease)<br>▪ Agitation or nervousness<br>▪ Confusion |

| | | |
|---|---|---|
| with increased risk of bleeding<br>▪ Anemia (low number of red blood cells)<br>▪ Infection<br>▪ Pneumonia<br>▪ Fever, with chills<br>▪ Swelling of hands and feet | ▪ Changes in vision<br>▪ Cough<br>▪ Skin rash | ▪ Severe brain injury and death<br>▪ Kidney damage that could require dialysis |

## Methotrexate

| **Likely**<br><br>(May happen in more than 20% of patients) | **Less Likely**<br><br>(May happen in less than 20% of patients) | **Rare, but Serious**<br><br>(May happen in less than 2% of patients) |
|---|---|---|
| ▪ Low number of white blood cells<br>▪ Infection<br>▪ Feeling tired<br>▪ Sensitivity to the sun (sunburn easily)<br>▪ Bruise easily<br>▪ Changes in skin<br>▪ Mouth and throat sores<br>▪ Loss of appetite<br>▪ Diarrhea<br>▪ Temporary hair loss | ▪ Nausea and vomiting<br>▪ Abdominal pain<br>▪ Fever, with chills<br>▪ Anemia (low number of red blood cells)<br>▪ Low number of platelets in the blood with increased risk of bleeding<br>▪ Kidney damage or failure<br>▪ High number of liver enzymes in the blood | ▪ Feeling dizzy<br>▪ Inflammation of the lungs<br>▪ Scarring of lung tissue<br>▪ Changes in vision<br>▪ Skin rash |

## Tacrolimus (FK506, Prograf®)

| **Likely**<br><br>(May happen in more than 20% of patients) | **Less Likely**<br><br>(May happen in less than 20% of patients) | **Rare, but serious**<br><br>(May happen in less than 2% of patients) |
|---|---|---|
| ▪ Kidney problems<br>▪ Low magnesium, calcium, and potassium in the blood<br>▪ High blood pressure<br>▪ Tremors (shaking)<br>▪ High cholesterol<br>▪ Low number of platelets in the blood with increased risk of bleeding<br>▪ Infection | ▪ Nausea and vomiting<br>▪ Liver problems<br>▪ Foggy thinking<br>▪ Trouble sleeping<br>▪ Unwanted hair growth<br>▪ Confusion<br>▪ Reversible posterior leukoencephalopathy syndrome [RPLS]/ Posterior reversible encephalopathy syndrome [PRES] (headache, confusion, seizures, and vision loss caused by very high blood pressure that comes on quickly) | ▪ Seizures<br>▪ Changes in vision<br>▪ Feeling dizzy<br>▪ The body stops making red blood cells (can lead to anemia)<br>▪ Lymphoproliferative disorder (the body makes too many lymphocyte cells) |

**It is very important that you do not eat grapefruit or drink grapefruit juice while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study.** Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

## Ixazomib (MLN9708)

| **Likely**<br><br>**(May happen in more than 10% of patients)** | **Less Likely**<br><br>**(May happen in less than 10% of patients)** | **Rare, but Serious**<br><br>**(May happen in less than 1% of patients)** |
|---|---|---|
| ▪ Low number of platelets in the blood with increased risk of bleeding<br>▪ Skin rash<br>▪ Feeling tired<br>▪ Feeling weak<br>▪ Nausea and vomiting<br>▪ Diarrhea<br>▪ Constipation<br>▪ Pain, numbness and tingling in hands and feet<br>▪ Anemia (low number of red blood cells)<br>▪ Low number of white blood cells<br>▪ Infection<br>▪ Loss of appetite<br>▪ Lung infection (pneumonia) | ▪ Changes in levels of potassium, calcium, sodium, and magnesium in the blood<br>▪ Flu-like symptoms such as chills, sore throat, runny nose, and sinus and throat infections<br>▪ Kidney failure that can require dialysis<br>▪ Shingles virus | ▪ Rash with skin peeling and mouth sores that can lead to death<br>▪ Posterior reversible encephalopathy syndrome (PRES) (headache, confusion, seizures and vision loss caused by very high blood pressure that comes on quickly)<br>▪ Progressive multifocal leukoencephalopathy (PML), a rare infection in the brain caused by a virus[1]<br>▪ Inflammation of the spinal cord with damage to nerves<br>▪ Fast death of cancer cells that can hurt organs like the kidneys<br>▪ Heart muscle injury (congestive heart failure) or lung tissue damage that can lead to death<br>▪ Liver failure |

| | | |
|---|---|---|
| ▪ Muscle weakness<br>▪ Swelling of the hands, feet, ankles or lower legs<br>▪ Upset stomach or pain in the belly or back<br>▪ Low blood pressure | | |

[1]PML has been observed rarely (< 0.1%) in patients taking ixazomib. It is not known if ixazomib may contribute to the development of PML in this patient.

Researchers for other studies of ixazomib are still watching patients to see how well they do on it. For this reason, there may be side effects that we don't know about yet. Also, we don't know if the side effects in the **Less Likely** group are caused by ixazomib, the patient's disease, or other drugs.

**Ixazomib and bortezomib <u>should not</u> be taken if you have ever had an allergic reaction to boron or products that contain boron.** Other drugs and supplements may affect the way Ixazomib works. It's important to tell your doctor about all drugs and treatments (for example, over-the-counter medicines and vitamins) you are taking while you are in this study.

<u>Previous Experience with Bortezomib</u>

The doctors who are conducting the study have gained some experience with a similar conditioning regimen used earlier in this study. They found that some patients who received 4 doses of bortezomib suffered a higher rate of expected severe side effects (including death) within 30 days of transplant. Because of these unanticipated early complications, the study doctors have reduced the number of doses of bortezomib given as a part of this study to one for new patients.

<u>Risk to the Unborn</u>

The treatments in this study <u>have not</u> been proven to be safe at any stage of pregnancy or nursing (breast feeding). If you are pregnant or nursing, you can't join this study.

Women <u>and</u> men must refrain from all acts of vaginal sex (abstinence) or use **2 types** of effective birth control while receiving chemotherapy, drugs to prevent GVHD, and maintenance treatment. You must use effective birth control during the entire study and for 90 days after stopping maintenance treatment. Effective birth control is defined as the following:

1. Consistent use of birth control pills

2. Injectable birth control methods (Depo-Provera, Norplant)

3. Tubal sterilization or male partner who has undergone a vasectomy

4. Placement of an IUD (intrauterine device)

5. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

You do not need to use effective birth control only if you are a woman and cannot have children because you:

- Had an effective tubal ligation (your tubes were tied), OR
- Had a hysterectomy (your ovaries and uterus were removed), OR
- Went through menopause (post-menopausal; i.e., have not had a menstrual period for at least 12 consecutive months).

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children, or cause birth defects if you take them while you are pregnant or nursing.

Both women who can become pregnant and their male partners should use birth control while on this study and for 90 days after maintenance treatment is stopped. **If you or your partner becomes pregnant during this study, you must tell the study doctor immediately.**

Your doctor will discuss the risks to your unborn child and options with you.

It is important that females who aren't pregnant or nursing don't become pregnant while part of the study. If you are a woman and become pregnant while on this study, we will stop the maintenance treatment drug right away.

Your study doctor will watch your health closely while you are pregnant.

- **Females who join the study**

If you are female and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you're in the study. Some women might experience irregular menstrual cycles or their cycle might stop forever. This doesn't mean that you can't become pregnant. You must still use 2 effective forms of birth control during the study and continue with it for 90 days after you finish maintenance treatment.

Be sure to talk with your doctor about options for fertility planning, like storing your eggs, before starting chemotherapy treatment.

- **Males who join the study**

If you are male, your body may not be able to produce sperm (become sterile). Be sure to talk with your doctor about options for fertility planning, like banking your sperm, before starting chemotherapy treatment.

**Risks of Transplant**

The following problems may happen after transplant. These problems might happen if you have a transplant as part of the study or as standard care:

Graft-Versus-Host Disease (GVHD)

GVHD develops when the white blood cells, which are called T cells, in the donor cells attack your body. You are more likely to get GVHD if your donor's tissue does not closely match your tissue.

There are 2 kinds of GVHD: acute and chronic. Acute GVHD usually develops within the first 3 months after transplant. Chronic GVHD usually develops later and lasts longer.

You may experience these side effects with acute GVHD:

- Skin rash
- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Diarrhea
- Abdominal (stomach area) pain
- Problems with your liver (your doctor will run tests for this)
- Infection

You may experience these side effects with chronic GVHD:

- Skin rash
- Hair loss

- Thickened skin
- Joint stiffness (knees, elbows, fingers)
- Dry eyes
- Dry mouth
- Liver disease (your doctor will run tests for this)
- Weight loss
- Diarrhea
- Infection

We don't know for sure if you will develop acute or chronic GVHD. The chance that you will get GVHD is 10-30%. This means that 10 to 30 people out of 100 might develop it. Your doctor will watch you closely for GVHD and treat it if it happens.

To know for sure if you have acute or chronic GVHD, we may do a biopsy of your skin. A biopsy is where we take a small piece of your skin and look at it under a microscope for signs of GVHD. There's a small chance that we might also do a biopsy of your intestine and liver. Risks of biopsy may include pain, infection, or bleeding.

In most cases, GVHD can be treated. If GVHD does not respond to the drugs, your doctor will talk with you about other treatment options. If you choose a different treatment option, we will give you information about the side effects.

You may need to be treated for GVHD for many months or years. GVHD treatments can cause your immune system to become very weak if it goes on for a long time. This means you may develop more infections and need to be admitted to the hospital often. GVHD can be very serious and hard to treat. It might also cause death.

<u>Slow recovery of blood counts</u>

The red blood cells, white blood cells, and platelets can be slow to recover after transplant. Until your blood counts recover, you will need blood and platelet transfusions. You'll be at risk for bleeding and infections. We may give you a drug called **Filgrastim** to speed up the recovery of the white blood cells as much as possible and lower the chance of bleeding and infections.

<u>Graft (donor cells) failure or rejection</u>

Some patients' bodies reject the donor cells (graft) with an allogeneic transplant. Also, a certain amount of your old blood and marrow cells will remain in your body.

If your body rejects the donor cells, your doctor may need to give you a donor lymphocyte infusion (DLI). A DLI is an extra dose of the donor cells. You may also get another transplant, but this is rare. If you need a DLI or second transplant, your doctor will explain the risks and benefits.

Damage to the vital organs in your body

Your vital organs include your heart, lungs, liver, intestines, kidneys, bladder and brain. The chemotherapy and GVHD drugs may hurt these organs. You may develop lung problems from chemotherapy or an infection.

Some patients can have veno-occlusive disease (VOD) of the liver. Patients with VOD become jaundiced (yellow skin), have problems with their liver, retain too much water (feel swollen and uncomfortable), and have stomach swelling and pain.

If there is serious damage to your vital organs, you may have to stay in the hospital longer or return to the hospital after your transplant. Many patients get better, but these complications can cause permanent damage to your organs or death.

Serious infections

It may take many months for your immune system to recover from the chemotherapy, GVHD and maintenance therapy drugs. There is an increased risk of infection during this time when your body is healing. We will give you drugs to reduce the chance of infection, but they may not work. If you have an infection, you may have to stay in the hospital longer or return to the hospital after transplant. Many patients get better, but some infections can cause death.

Return of disease

Your disease may come back even if the transplant is successful at first. Your doctor will discuss your treatment options with you if your disease returns and you are removed from study.

Development of a new cancer

In rare cases, a new type of cancer may develop from the donor cells. The risk of developing a new cancer after allogeneic transplant is less than 2% (1 or 2 patients (or fewer) out of 100).

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect

your decision to take part in the study. We may learn new things about allogeneic transplants, GVHD prevention treatment, or maintenance treatment that might make you want to stop being in the study. If this happens, we will let you know so you can decide if you want to continue in the study.

Other Treatments or Medicines

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study.

For more information about risks and side effects, ask your study doctor.

## 7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive non-transplant treatments or an autologous or an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant.
- An allogeneic (donor) blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)
- No treatment for your blood cancer at this time
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

## 8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about drugs used to treat multiple myeloma.

This information could help people with multiple myeloma who may need a transplant in the future.

## 9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

## 10. Privacy, Confidentiality and Use of Information

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

All your medical and demographic information (such as race and ethnicity, gender and household income) will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment. In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

Information about your transplant from your original medical records may be seen or sent to national and international transplant registries, including:

- /Institution/
- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)
- The Food and Drug Administration (FDA)
- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN)
- Data and Safety Monitoring Board (DSMB), not part of /Institution/
- Study investigators.
- Millennium, its collaborators or designees

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this study has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered studies.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Data regarding your clinical situation, including follow-up after 2 years, may be obtained from the CIBMTR, which captures information on all U.S. transplants.

For questions about access to your medical records, please contact /name/ at /number.

## 11. Ending Your Participation

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

You could have serious health risks if you stop treatment during the conditioning process before you receive your transplant. If you stop taking the immune suppressing drugs (see **Section 6: Risks and Discomforts**) too soon after transplant, your body could reject the donor stem cells or you could develop serious complications and possibly die.

We ask that you talk with the research doctor and your regular doctor before you leave the study. Your doctors will tell you how to stop safely and talk with you about other treatment choices.

If you decide to leave this study after getting the study treatment, or are asked to leave by your doctor for medical reasons, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

## 12. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get all available medical treatment if you are injured from taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case you are injured in this study, you do not lose any of your legal rights to ask for or receive payment by signing this form.

## 13. Compensation or Payment

You will not be paid for your participation in this research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial.

Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc. or others, may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

## 14. Costs and Reimbursements

Most of the visits for this research study are standard medical care for your allogeneic transplant and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study. The study drugs bortezomib, ixazomib, and placebo will be provided by Millennium at no cost to you or your insurance.

You or your insurance will not be charged for optional blood samples for research on this study. You will not pay for any extra tests that are being done for the study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out if they will pay.

For questions about your costs, financial responsibilities, and/or medical insurance coverage for your transplant and this study, please contact /Center/ Financial Counselor at /Number/.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

## 15. For More Information

If you need more information about this study, or if you have problems while taking part in this study, you can contact the study doctor or his/her staff.

They can be reached at the telephone numbers listed here:

[*Insert name and contact details*]

## 16. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

The ethical aspects of this study have been reviewed and approved by *[name of IRB]*.

## 17. Blood and Tissue Samples for Future Research (Optional)

This section of the informed consent form is about future research studies that will use blood and tissue samples from people who are taking part in the main study. You may choose to give samples for these future research studies if you want to. You can still be a part of the main study even if you say 'no' to give samples for future research studies.

Researchers are trying to learn more about how the human body processes the drugs used for transplant and how the body recovers after transplant. This research is meant to gain knowledge that may help people in the future and make transplants even more successful.

If you agree to provide blood and tissue samples, here is what will happen:

- We will collect extra blood samples at the same time you have routine blood tests done. The amount of blood collected from you is about 7 teaspoons (36 mL) each time.
- We will collect blood samples at seven different dates in the study (see **Tables 3 and 4**):
    - 2 weeks or less before transplant
    - 4 weeks after transplant
    - 2 weeks before maintenance treatment is started
    - Cycles 2, 5 and 10 of maintenance treatment
    - 28 days or less after your last dose of maintenance treatment
- We will collect three bone marrow tissue samples at the same time you have routine bone marrow biopsies done. The amount of tissue collected from you is about 2 teaspoons (10 mL) each time. We will collect samples at three different dates in the study (see **Tables 3 and 4**):
    - 2 weeks or less before transplant

- 2 weeks before maintenance treatment is started
- 28 days or less after your last dose of maintenance treatment

- Some of your samples will be stored and some will be used for research right now. The samples to be stored will be sent to the BMT CTN Repository for processing and storage. A repository is a place that protects, stores, and sends out samples for approved research studies. All seven of the blood samples will be sent to the BMT CTN Repository to be stored. A small amount of three out of the seven blood samples will be sent to Roswell Park Cancer Institute for a research study looking at how fast your immune system recovers after the transplant. There were will be no additional blood samples collected. All research samples, including the ones that will be stored, will be given a barcode that cannot be linked to you by future researchers testing your samples. The link between your patient identification and your sample barcode will be held in your study records at [Insert Site Name] only.

- The liquid bone marrow collected will be sent to the BMT CTN Repository and to Roswell Park Cancer Institute for testing. The bone marrow samples going to the BMT CTN Repository will be processed and stored similar to blood samples. The bone marrow samples sent to Roswell Park Cancer Institute will be tested to detect multiple myeloma cells. This test is called minimal residual disease and it will assist in understanding how much this treatment is controlling the cancer.

- Materials stored in the Repository will be used mainly by clinicians and researchers in the BMT CTN network. In the future, the unused research samples and clinical data will be made available outside of this network.

- Researchers can apply to study the materials stored in the Repository. The BMT CTN Steering Committee and/or the BMT CTN Executive Committee must approve each request before they will share samples or information with researchers. This is to make sure that the investigators requesting the samples are qualified, and that the research is of high quality.

- DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

  If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a shared, public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the

National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples.

Some general things you should know about letting us store your blood samples for research are:

- We will only store samples from people who give us permission.
- Research is meant to gain knowledge that my help people in the future. You will not get any direct benefit from taking part. Additionally, you or your doctor will not be given results and they will not be added to your medical record.
- A possible risk is the loss of confidentiality about your medical information. We will use safety measures with both your samples and clinical information to make sure that your personal information will be kept private. The chance that this information will be given to someone else is extremely small.
- Your blood and tissue samples will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future. You will not get paid for any samples or for any products that may be developed from current or future research.

**You can change your mind at any time about allowing us to use your samples and health information for research**.

We ask that you contact [Principal Investigator] in writing and let him/her know you do not want us to use your research samples or health information for research. His/her mailing address is on the first page of this form. However, samples and information that have already been shared with other researchers cannot be taken back or destroyed.

**Making Your Choice**

Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

## Statement of Consent for Research Samples

The purpose of storing blood and tissue samples, the procedures involved, and the risks and benefits have been explained to me. I understand that if I provide consent, the liquid part of my bone marrow will be assessed for minimal residual disease and that my blood samples will be used to assess how quickly my immune system recovers. I have asked all the questions I have at

this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood and tissue for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that my blood, tissue, and information can be stored indefinitely by the BMT CTN and/or NHLBI Repositories for research to learn about, prevent, or treat health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

**Blood**

❑ I agree to allow my blood samples to be stored for future and immune reconstitution research.

❑ I do not agree to allow my blood samples to be stored for future and immune reconstitution research.

**Bone marrow**

❑ I agree to allow my bone marrow tissue samples to be stored for future and MRD research.

❑ I do not agree to allow my bone marrow tissue samples to be stored for future and MRD research.

_____ _____

Signature Date

**Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purpose**

**A. Purpose**:

As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Phase II, Double-blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Cell Transplantation for High Risk Multiple Myeloma

**B. Individual Health Information to be Used or Disclosed**:

My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example, date of birth, sex, weight)
- Medical history (for example, diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example, blood tests, biopsy results)

**C. Parties Who May Disclose My Individual Health Information**:

The researcher and the researcher's staff may collect my individual health information from:

[*List hospitals, clinics or providers from which health care information can be requested*]

**D. Parties Who May Receive or Use My Individual Health Information**:

The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

Dr. Parameswaran Hari, Co-Principal Investigator

Dr. Taiga Nishihori, Co-Principal Investigator

Dr. Qaiser Bashir, Co-Principal Investigator

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

Millennium, its collaborators or designees

Study Sponsors

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Data and Coordinating Center
- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.

**E. Right to Refuse to Sign this Authorization**:

I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

**F. Right to Revoke**:

I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, t he researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

**G. Potential for Re-disclosure**:

My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

## H. Genetic Information Nondiscrimination Act (GINA)

A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

## I. This authorization does not have an expiration date.

**TITLE:** A Multi-Center Phase II, Double-Blind Placebo Controlled Trial of Maintenance Ixazomib after Allogeneic Hematopoietic Cell Transplantation for High Risk Multiple Myeloma

**PROTOCOL NUMBER:** BMT CTN #1302

**PRINCIPAL INVESTIGATOR:**

Name:

Address:

Email:

Phone:

Fax:

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

| | |
|---|---|
| Participant Name | Date |
| Signature | Date |

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

| | |
|---|---|
| Name of Counseling Physician | Date |
| Signature of Counseling Physician | Date |

# APPENDIX C
# LABORATORY PROCEDURES

# LABORATORY PROCEDURES

## Collection of OPTIONAL Samples for Future Ancillary Studies

Bone marrow aspirate and blood will be collected from patients who signed consent to provide samples for minimal residual disease (MRD) testing and future research. Sample collection will be done at the transplant center and will require minimum processing. Once the samples are collected at specified time points they will be shipped on the day of collection to the BMT CTN Central Processing Laboratory for final processing and storage at the BMT CTN Research Biologic Repository, and for bone marrow aspirates an aliquot will be submitted to the Department of Flow and Image Cytometry at Roswell Park Cancer Institute. These samples will be tracked through GlobalTrace.

- **Bone Marrow Aspirate Samples**
  Patients who consented for marrow sample collection for MRD and future research studies will have 10 mL of bone marrow aspirate collected at three time points (1) baseline (preferably in one single procedure along with standard of care aspirate collection prior to allogeneic transplant), (2) prior to initiation of maintenance (time of randomization), and (3) $\leq$ 28days after the last dose of study drug during maintenance. Samples will be collected in heparin anticoagulant coated tubes. Two aliquots of bone marrow aspirate will be collected; the first aliquot of 2-4mL will be used for MRD testing, the second aliquot of 6-8mL will be collected for future research. The first tube for MRD testing will be shipped to the project laboratory at Roswell Park Cancer Institute (RPCI). The second tube will be shipped to the BMT CTN Central Processing Laboratory for further processing and storage. Both tubes are shipped at ambient temperature. These samples will be tracked through GlobalTrace.

- **Peripheral Blood Research Specimens**
  Patients who consented for peripheral blood sample collection for future research studies will have 36 mL blood samples collected at 7 time points: (1) baseline (at enrollment), (2) 28 days after transplant (3) prior to initiation of maintenance (time of randomization), (4-6) at the start of the 2nd, $5^{th}$ and $10^{th}$ cycle of maintenance therapy and (7) $\leq$ 28 days after the last dose of study drug during maintenance. An aliquot of 10mL from the 30 mL collected for PBMC preparation will be directed to immune reconstitution studies at the RPCI laboratory. The time points that the PBMC sample should be aliquotted are:

  (1) prior to initiation of maintenance (time of randomization), (2) at the start of $5^{th}$ cycle of maintenance therapy and (3) $\leq$ 28 days after the last dose of study drug during maintenance.

## *SCHEDULE OF LABORATORY EVALUATIONS*

| | Type of Sample | Type of Processing | Dates Samples Obtained | Shipping Specifications | Storage Location |
|---|---|---|---|---|---|
| **Patient Research Bone Marrow Aspirate** | 10 mL bone marrow aspirate | Collect bone marrow aspirate sample and place in a 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.<br><br>No additional sample processing is required. | At enrollment, ≤ 14 days prior to initiation of maintenance[1], and ≤ 28 days after the last dose of maintenance study drug. | Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of marrow aliquots. | BMT CTN Research Repository |
| **Bone Marrow Aspirate for MRD testing** | 2-4 mL bone marrow aspirate (aliquot of 2-4 mL from the initial bone marrow aspirate collected, as above) | Processed as part of the original 10 mL bone marrow aspirate as described above. | At enrollment, ≤ 14 days prior to initiation of maintenance[1], and ≤ 28 days after the last dose of maintenance study drug. | Bone marrow aspirate sample will be shipped at ambient temperature on the day of collection, to the **Department of Flow and Image Cytometry** at Roswell Park Cancer Institute by priority overnight FED EX delivery for immunophenotyping. | - |

| | Type of Sample | Type of Processing | Dates Samples Obtained | Shipping Specifications | Storage Location |
|---|---|---|---|---|---|
| **Patient Research Peripheral Blood Specimen (Serum)** | 6 mL peripheral blood | Collect blood sample in a Red/Gray Top BD SST™ Tube with Silica Clot Activator & Polymer Gel. Let sample sit upright in rack for 30 minutes. Centrifuge for 10 minutes. Gel barrier will form separating the serum specimen from clot. Prepare tube for transport along with other research samples. | At enrollment, 28 days after transplant, ≤ 14 days prior to initiation of maintenance[1], at the start of the 2nd, 5th, and 10th cycles of maintenance therapy, and ≤ 28 days after the last dose of maintenance study drug. | Serum blood tube will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of serum aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository is detailed in the 1302 Research Sample Guide. | BMT CTN Research Repository |
| **Patient Research Peripheral Blood Specimen (PBMC)** | 30 mL peripheral blood | Collect peripheral blood sample in three 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.<br><br>No additional sample processing is required. | At enrollment, 28 days after transplant, ≤ 14 days prior to initiation of maintenance[1], at the start of the 2nd, 5th, and 10th cycles of maintenance therapy, and ≤ 28 days after the last dose of maintenance study drug. | PBMC blood tubes will be shipped at ambient temperature on the day of collection, to the BMT CTN Research Repository by priority overnight FED EX delivery for processing and final frozen storage of isolated viable PBMC aliquots. Guidelines for specimen handling and shipment to the BMT CTN Central Processing Laboratory/BMT CTN Research Repository is detailed in the 1302 Research Sample Guide. | BMT CTN Research Repository |

| | Type of Sample | Type of Processing | Dates Samples Obtained | Shipping Specifications | Storage Location |
|---|---|---|---|---|---|
| **Peripheral Blood Specimen for Immune-reconstitution**<br><br>**(PBMC)** | 10 mL peripheral blood[2] | Collect peripheral blood sample in one 10 mL fill, green top plastic BD Vacutainer® tube, containing Sodium-Heparin anticoagulant. Gently mix sample by inversion 8-10 times to mix sample well with heparin anticoagulant.<br><br>No additional sample processing is required. | ≤ 14 days prior to initiation of maintenance[1], at the start of the 5th cycle of maintenance therapy, and ≤ 28 days after the last dose of maintenance study drug. | PBMC sample will be shipped at ambient temperature on the day of collection, to the **Department of Flow and Image Cytometry** at Roswell Park Cancer Institute by priority overnight FED EX delivery for immunophenotyping. | - |

[1]Optional blood and bone marrow samples must be collected ≤ 14 days prior to the initiation of maintenance therapy. The samples should be collected AFTER randomization and BEFORE initiation of maintenance therapy, however samples collected prior to randomization that fall within this window may be accepted.
[2]The collection of PBMC for immune reconstitution will be an aliquot of the 30 mL collected for future research at the time points specified above.

# APPENDIX D
# HCT-SPECIFIC COMORBIDITY INDEX SCORE

## HCT-SPECIFIC COMORBIDITY INDEX SCORE

| Comorbidities | Definition | Score |
|---|---|---|
| Migraine/headache | | **0** |
| Osteoporosis | | **0** |
| Osteoarthritis | | **0** |
| Hypertension | | **0** |
| Gastrointestinal | Including inflammatory bowel disease | **0** |
| Mild pulmonary | DLCo and/or $FEV_1$ >80% or<br>Dyspnea on moderate activity | **0** |
| Mild renal | Serum creatinine 1.2-2 mg/dl | **0** |
| Endocrine | | **0** |
| Bleeding | | **0** |
| Coagulopathy | Deep venous thrombosis or pulmonary embolism | **0** |
| Asthma | | **0** |
| Arrhythmia | | **1** |
| Myocardial | Coronary artery disease, congestive HF, history of medically documented MI, EF≤50% | **1** |
| Mild hepatic | Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN | **1** |
| Cerebro-vascular accident | History of transient ischemic attack or cerebro-vascular accident | **1** |
| Morbid obesity | | **1** |
| Diabetes | Requiring treatment | **1** |
| Depression/anxiety | | **1** |
| Infection | Requiring continuation of treatment after Day 0 | **1** |
| Rheumatologic | SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica | **2** |
| Moderate pulmonary | DLCo and/or $FEV_1$ 66-80% or<br>Dyspnea on slight activity | **2** |
| Peptic ulcer | Patients who have required treatment | **2** |
| Moderate-severe renal | Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation | **2** |
| Valvular heart disease | Except mitral valve prolapse | **3** |
| Prior solid tumor | Requiring treatment with chemotherapy | **3** |
| Moderate-severe hepatic | Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN | **3** |
| Severe pulmonary | DLCo and/or $FEV_1$ ≤65% or<br>Dyspnea at rest or requiring oxygen | **3** |

Total score is the sum of all comorbidities present at time of transplantation.

# APPENDIX E
# KARNOFSKY PERFORMANCE STATUS SCALE

## KARNOFSKY PERFORMANCE STATUS SCALE

| **Index** | **Specific Criteria** | **General** |
|---|---|---|
| **100** | Normal, no complaints, no evidence of disease. | Able to carry on normal activity; no special care needed. |
| **90** | Able to carry on normal activity, minor signs or symptoms of disease. | |
| **80** | Normal activity with effort, some signs or symptoms of disease. | |
| **70** | Care for self, unable to carry on normal activity or to do work. | Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed. |
| **60** | Requires occasional assistance from others but able to care for most needs. | |
| **50** | Requires considerable assistance from others and frequent medical care | |
| **40** | Disabled, requires special care and assistance. | Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing. |
| **30** | Severely disabled, hospitalization indicated, but death not imminent. | |
| **20** | Very sick, hospitalization necessary, active supportive treatment necessary. | |
| **10** | Moribund | |
| **0** | Dead | |

# APPENDIX F
# NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

## NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease.

| Class | Functional Capacity | Objective Assessment |
|---|---|---|
| **I** | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease. |
| **II** | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease. |
| **III** | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease. |
| **IV** | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

# APPENDIX G
# HUMAN SUBJECTS

# HUMAN SUBJECTS

## 1. Subject Consent

A conference will be held with the patient and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the Principal Investigator or other designated physician. Potential risks associated with the study interventions should be discussed as objectively as possible. Consent will be obtained using an IRB-approved consent.

The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval.

## 2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

## 3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of MM in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

# APPENDIX H
# KNOWN ANTICIPATED RISKS OF BORTEZOMIB

**Table H-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term**

| System Organ Class- Observed Incidence | Preferred Term |
|---|---|
| **Blood and Lymphatic System Disorders** | |
| Most common | Thrombocytopenia*, anemia* |
| Very common | Neutropenia* |
| Common | Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia |
| **Cardiac Disorders** | |
| Common | Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive* |
| Uncommon | Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure± |
| **Ear and Labyrinth Disorders** | |
| Uncommon | Deafness, hearing impaired |
| **Eye Disorders** | |
| Common | Blurred vision, conjunctivitis, conjunctival hemorrhage |
| **Gastrointestinal Disorders** | |
| Most common | Constipation, diarrhea*, nausea, vomiting* |
| Very common | abdominal pain (excluding oral and throat) |
| Common | Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage*, lower gastrointestinal hemorrhage*± rectal hemorrhage |
| Uncommon | Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, esophagitis, enterocolitis, diarrhea hemorrhagic, acute pancreatitis*, intestinal obstruction |
| **General Disorders and Administration Site Conditions** | |
| Most common | Fatigue, pyrexia |
| Very common | Chills, edema peripheral, asthenia |
| Common | Neuralgia, lethargy, malaise, chest pain, mucosal inflammation* |
| Uncommon | Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication |
| **Hepatobiliary Disorders** | |
| Uncommon | Hyperbilirubinemia, hepatitis*± |

**Table H-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term**

| System Organ Class- Observed Incidence | Preferred Term |
|---|---|
| **Immune System Disorders** | |
| Uncommon | Drug hypersensitivity, angioedema |
| **Infections and Infestations** | |
| Very common | Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster* |
| Common | Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bacteremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection |
| Uncommon | Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal esophagitis± |
| **Injury, Poisoning, and Procedural Complications** | |
| Common | Fall |
| Uncommon | Subdural hematoma |
| **Investigations** | |
| Common | Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased* |
| Uncommon | Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased* |
| **Metabolism and Nutritional Disorders** | |
| Very common | Decreased appetite, anorexia, dehydration* |
| Common | Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia* |
| **Musculoskeletal and Connective Tissue Disorders** | |
| Very common | Bone pain, myalgia, arthralgia, back pain |
| Common | Muscular weakness |
| Uncommon | Limb discomfort |
| **Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)** | |
| Uncommon | Tumor lysis syndrome* |

**Table H-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term**

| System Organ Class- Observed Incidence | Preferred Term |
|---|---|
| **Nervous System Disorders** | |
| Most common | Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC) |
| Very common | Paresthesia, dizziness excluding vertigo, headache |
| Common | Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia |
| Uncommon | Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ϕ |
| **Psychiatric Disorders** | |
| Very common | Anxiety, insomnia |
| Common | Confusional state |
| Uncommon | Delirium |
| **Renal and Urinary Disorders** | |
| Common | Renal impairment*, renal failure*, hematuria |
| Uncommon | Micturition disorder |
| **Respiratory, Thoracic, and Mediastinal Disorders** | |
| Very common | Cough, dyspnea |
| Common | Epistaxis, dyspnea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary edema* |
| Uncommon | Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar hemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain |
| **Skin and Subcutaneous Tissue Disorders** | |
| Very common | Rash, alopecia |
| Common | Rash pruritic, rash erythematous, urticaria, petechiae |
| Uncommon | Cutaneous vasculitis, leukocytoclastic vasculitis± |
| **Vascular Disorders** | |
| Common | Hypotension*, orthostatic hypotension |
| Uncommon | Cerebral hemorrhage* |

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 16.

Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

* Fatal outcomes have been reported.

± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

ϕ Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.

| **Table H-2 Reports of Adverse Reactions From Postmarketing Experience** | |
|---|---|
| **System Organ Class- Preferred Term** | **Observed Incidence[a]** |
| **Blood and lymphatic system disorders** | |
| *Disseminated intravascular coagulation* | Rare |
| **Cardiac Disorders** | |
| *Atrioventricular block complete* | Rare |
| *Cardiac tamponade* | Rare |
| **Ear and labyrinth disorders** | |
| *Deafness bilateral* | Rare |
| **Eye Disorders** | |
| *Ophthalmic herpes* | Rare |
| *Optic neuropathy* | Rare |
| *Blindness* | Rare |
| **Gastrointestinal Disorders** | |
| *Acute pancreatitis* | Rare |
| *Ischemic colitis* | Rare |
| **Hepatobiliary disorders** | |
| *Hepatitis* | Uncommon |
| *Liver failure* | Unknown |
| **Infections and infestations** | |
| *Herpes meningoencephalitis* | Rare |
| *Septic shock* | Rare |
| *Progressive multifocal leukoencephalopathy* | Very rare |
| **Immune System Disorders** | |
| *Angioedema* | Rare |
| **Nervous System Disorders** | |
| *Autonomic neuropathy* | Rare |
| *Dysautonomia* | Unknown |
| *Encephalopathy* | Rare |
| **Respiratory, thoracic and mediastinal disorders:** | |
| *Acute diffuse infiltrative pulmonary disease[b]* | Rare |
| *Acute respiratory distress syndrome (ARDS)* | Rare |
| *Interstitial pneumonia* | Rare |
| *Lung infiltration* | Rare |

| | |
|---|---|
| *Pneumonitis* | Rare |
| *Pulmonary hypertension* | Rare |
| **Skin and subcutaneous system disorders** | |
| *Acute febrile neutrophilic dermatosis* | Unknown |
| *Toxic epidermal necrolysis* | Unknown |

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 16.

a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000 ); very rare (< 1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

# APPENDIX I
# ADVERSE EVENT REPORTING

# APPENDIX I

# ADVERSE EVENT REPORTING

## I.1 Adverse Event Reporting

Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms in AdvantageEDC.

The calendar-driven forms are those that appear in the AdvantageEDC Forms Grid for each enrolled patient at designated time points (e.g., Day 28 post transplant) throughout the course of the study. Completion of a calendar-driven form is expected by the Target Date for the given assessment period.

Calendar-driven forms for the BMT CTN 1302 study are as follows:

- **Toxicity Form**: this form documents all expected toxicities for the BMT CTN 1302 study; each toxicity is also assigned a grade, based on the NCI CTCAE Version 4.0.
- **Hematology/Chemistry Form**: this form documents selected hematology (CBC/differential) and blood chemistry results.
- **Follow-Status Form**: this form documents the status of each patient at various intervals on the study.

Event-driven forms must be completed when a certain event triggers the appearance of the form in the AdvantageEDC Forms Grid. Most often the event-driven form is triggered by information entered on the Follow-up Status Form. Event-driven forms for the BMT CTN 1302 study are as follows:

- **Re-Admission/Hospitalization Form**: this form documents all hospital admissions, *including* the admission for transplant for this study.
- **Infection Form**: this form documents infections from Day 0 (date of transplant) through the 1-year post-transplant follow-up period.
- **Secondary Graft Failure Form**: this form captures the details associated with secondary graft failure. DO NOT report secondary graft failure as an Unexpected, Grade 3-5 Adverse Event.
- **Progression/Relapse Form**: the form captures detailed information associated with progression or relapse of the primary disease. DO NOT report progression or relapse as an Unexpected, Grade 3-5 Adverse Event.
- **Death Form**: this form documents the death of a patient from the time of study enrollment and randomization through the 1-year post-transplant follow-up period.
- **Bortezomib SAE Screening Form**: this form captures basic information on all SAEs occurring from the time of bortezomib administration through 30 days after.
- **Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, regardless of attribution to any of the study interventions. These forms are also used to collect information on any SAE event required by the additional adverse event reporting requirements. These events require expedited

reporting and will be reviewed by the Medical Monitor at the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.

## I.2 Reporting Expected Toxicities

Expected toxicities for all patients enrolled on BMT CTN 1302 will be collected on the BMT CTN 1302 Calendar-Driven Toxicity Form and some of the event-driven forms (Infection, Readmission/Hospitalization, Progression/Relapse, Graft Failure and Death forms). Any grade 4 expected event not collected on the calendar-driven toxicity or specified event- driven form must be reported through the expedited AE reporting system in AdvantageEDC.

## I.3 Reporting Second Primary Malignancies

**All second primary malignancies (SPMs), excluding non-melanoma skin cancers, experienced by participants enrolled on the BMT CTN 1302 study must be reported within three business days of knowledge of the event using the Adverse Event forms (AE1-AE6) in AdvantageEDC.** The Event Description of the Adverse Event forms should include histologic type. Reporting of SPMs in AdvantageEDC is required until all patients have completed 2 years of follow up.

### I.3.1 Adverse Event Reporting Following an SPM

Adverse Event reporting following an SPM is dependent on the treatment received for the reported SPM.

- If a patient experiences an SPM resulting in permanent discontinuation of maintenance and initiation of non-protocol systemic therapy, Unexpected Grade 3-5 Adverse Events and events listed in Appendix I are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of maintenance.
- If a patient experiences an SPM that does *not* result in permanent discontinuation of maintenance, Adverse Events will continue to be reported as per section 4.4.3 and Appendix I of the protocol.
- Requests to discontinue Adverse Event Reporting for events that do not meet the criteria above will be considered on a case by case basis.

## I.4 Reporting Unexpected, Grade 3-5 Adverse Events

**All Unexpected, Grade 3-5 Adverse Events should be reported for every patient enrolled on the study from the time of enrollment until 2 years post transplant**. Additional Adverse Event reporting applies to patients dependent on the treatment received on the study. Determination of the expectedness of adverse events should be differentiated between the initial transplant or maintenance therapy at the discretion of the investigator. For example, oral mucositis would be an expected risk associated with transplantation, but the investigator should assess the expectedness for oral mucositis during maintenance.

### I.4.1 Adverse Event Reporting Following Progression

If a patient meets the protocol-defined definition of progression (see Chapter 3), Unexpected Grade 3-5 Adverse Events and events listed in Appendix I are no longer required to be reported on the Adverse Event Form once the patient is more than 28 days from their last dose of maintenance. However, SPMs should continue to be reported within three business days of the knowledge of the event through the end of the study follow-up period.

## I.5 Adverse Event Reporting For Bortezomib

This section outlines the adverse event reporting requirements for all patients receiving Bortezomib on BMT CTN 1302. Millennium Pharmaceuticals, Inc. (MPI) is supplying bortezomib for all patients enrolled on this study. MPI has additional adverse event reporting requirements for all patients who receive study bortezomib.

**In addition to the standard BMT CTN guidelines for reporting adverse events** (see Chapter 4, Section 4.4.3), MPI is requiring the reporting of **all** Serious Adverse Events (SAEs) that occur **from the time of bortezomib administration (Day -3) through 30 days after.** This includes events meeting the definition of a Serious Adverse Event, per 21 CFR 312.32, as follows:

**Serious Adverse Event:** A serious adverse event (SAE) is any adverse event that results in one of the following outcomes, regardless of causality and expectedness:

- **Results in death**
- **Is life-threatening.** Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity.** Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect;** or
- **Is an important medical event** when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a Serious Adverse Event). Any event is considered a Serious Adverse Event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

### I.5.1 Reporting Timelines for Events Occuring During Bortezomib Reporting Period

- Fatal and Life-Threatening events must be reported in AdvantageEDC within 24 hours, of the investigator's observation or awareness of the event.
- All Other Serious events (non-fatal/non-life-threatening) must be reported in AdvantageEDC within 3 calendar days of the investigator's observation or awareness of the event.

### I.5.2 How to Report Serious Adverse Events During Bortezomib Reporting Period

All SAEs will be reported in AdvantageEDC by completing the Bortezomib SAE Screening Form. All SAEs also require completion of the Adverse Event Forms (AE1-AE6), unless any of the following SAEs are determined to be unrelated or unlikely related to the bortezomib, then the Adverse Event Forms are not required:

- ***Neutropenia***
- ***Thrombocytopenia***
- ***Anemia***
- ***Minor bleeding episodes (i.e. epistaxis)***
- ***Graft-versus-host disease (GVHD)***
- ***Graft failure***
- ***Hepatic veno-occlusive disease (VOD)***
- ***Thrombotic microangiopathy (TMA)***

Accurate completion of the Bortezomib SAE and/or Adverse Event forms will allow the DCC to provide MPI with the details they require to fully understand each event, so it is *critical* that all fields are filled in and comprehensive supporting source documents for the event (PHI redacted) are uploaded to the appropriate forms.

If an adverse event does not meet the criteria of an SAE, it will require reporting on the Adverse Event form if it is both unexpected and grade 3-5 based on the BMT CTN standard reporting guidelines.

## I.6 Adverse Event Reporting Beginning 30 Days After Bortezomib

This section outlines the adverse event reporting requirements for all patients beginning 30 days after the final dose of bortezomib until the first dose of maintenance. If the patient does not initiate

maintenance therapy, the requirements outlined within this section should be followed until 2 years post transplant.

Table I-1 lists adverse events and toxicities for this study, as well as the form in AdvantageEDC that is used to document the event.

**TABLE I-1: ADVERSE EVENTS FOR BMT CTN 1302 BEGINNING 30 DAYS AFTER BORTEZOMIB ADMINISTRATIONBY ORGAN SYSTEM**

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **AUDITORY DISORDERS** | | |
| **Hearing loss** | **Calendar-Driven** | **Toxicity** |
| **BLOOD AND LYMPHATIC DISORDERS** | | |
| **Anemia** | **Calendar-Driven** | **Toxicity** |
| **Neutropenia** | **Calendar-Driven** | **Toxicity** |
| **Thrombocytopenia** | **Calendar-Driven** | **Toxicity** |
| **Thrombotic thrombocytopenic purpura/ Thrombotic microangiopathy** | **Calendar-Driven** | **Toxicity** |
| **CARDIAC DISORDERS** | | |
| **Cardiac arrhythmia** | **Calendar-Driven** | **Toxicity** |
| **Hypertension** | **Calendar-Driven** | **Toxicity** |
| **Hypotension** | **Calendar-Driven** | **Toxicity** |
| **Left ventricular systolic dysfunction** | **Calendar-Driven** | **Toxicity** |
| **Myocardial infarction** | **Calendar-Driven** | **Toxicity** |
| **New or worsening heart failure** | **Calendar-Driven** | **Toxicity** |
| **Pericardial effusion** | **Calendar-Driven** | **Toxicity** |
| **Pericarditis** | **Event-Driven** | **Adverse Event Form** |
| **Peripheral edema** | **Calendar-Driven** | **Toxicity** |
| **Restrictive cardiomyopathy** | **Calendar-Driven** | **Toxicity** |
| **GASTROINTESTINAL DISORDERS** | | |
| **Abdominal pain** | **Calendar-Driven** | **Toxicity** |
| **Anorexia** | **Calendar-Driven** | **Toxicity** |
| **Constipation** | **Calendar-Driven** | **Toxicity** |
| **Diarrhea** | **Calendar-Driven** | **Toxicity** |
| **Dysgeusia (taste alteration)** | **Calendar-Driven** | **Toxicity** |
| **Dyspepsia (heartburn)** | **Calendar-Driven** | **Toxicity** |
| **Gastroenteritis** | **Calendar-Driven** | **Toxicity** |
| **Intestinal obstruction** | **Event-Driven** | **Adverse Event Form** |
| **Nausea** | **Calendar-Driven** | **Toxicity** |
| **Oral mucositis** | **Calendar-Driven** | **Toxicity** |
| **Vomiting** | **Calendar-Driven** | **Toxicity** |
| **GENERAL DISORDERS** | | |
| **Fatigue** | **Calendar-Driven** | **Toxicity** |

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **Fever** | **Calendar-Driven** | **Toxicity** |
| **HEPATOBILIARY/PANCREAS DISORDERS** | | |
| **Abnormal liver function tests** | **Calendar-Driven** | **Toxicity** |
| **Hepatitis** | **Event-Driven** | **Adverse Event Form** |
| **Liver failure** | **Event-Driven** | **Adverse Event Form** |
| **Pancreatitis** | **Calendar-Driven** | **Toxicity** |
| **HEMORRHAGIC DISORDERS** | | |
| **Intracranial** | **Event-Driven** | **Adverse Event Form** |
| **Gastrointestinal** | **Calendar-Driven** | **Toxicity** |
| **Genitourinary** | **Calendar-Driven** | **Toxicity** |
| **Pulmonary/Upper respiratory** | **Calendar-Driven** | **Toxicity** |
| **IMMUNE SYSTEM DISORDERS** | | |
| **Allergic reaction** | **Event-Driven** | **Adverse Event Form** |
| **Anaphylaxis (swelling of the skin and/or swelling of the face or throat)** | **Event-Driven** | **Adverse Event Form** |
| **INFECTIONS** | | |
| **Fungal infections of the mouth and throat** | **Event-Driven** | **Infection** |
| **Herpes virus/shingles** | **Event-Driven** | **Infection** |
| **Infections of the bladder, sinuses, throat, stomach and intestines, and skin** | **Event-Driven** | **Infection** |
| **Sepsis** | **Event-Driven** | **Infection** |
| **METABOLISM AND NUTRITION DISORDERS** | | |
| **Hypercalcemia** | **Calendar-Driven** | **Toxicity** |
| **Hyperglycemia** | **Calendar-Driven** | **Toxicity** |
| **Hypoglycemia** | **Calendar-Driven** | **Toxicity** |
| **Hypokalemia** | **Calendar-Driven** | **Toxicity** |
| **Hyponatremia** | **Calendar-Driven** | **Toxicity** |
| **Tumor lysis syndrome** | **Event-Driven** | **Adverse Event Form** |
| **MUSCULOSKELETAL AND TISSUE DISORDERS** | | |
| **Arthralgia** | **Calendar-Driven** | **Toxicity** |
| **Myalgia** | **Calendar-Driven** | **Toxicity** |
| **Muscle weakness (generalized or specific area)** | **Calendar-Driven** | **Toxicity** |
| **NERVOUS SYSTEM DISORDERS** | | |
| **Anxiety** | **Calendar-Driven** | **Toxicity** |
| **Confusion** | **Calendar-Driven** | **Toxicity** |
| **Depression** | **Calendar-Driven** | **Toxicity** |
| **Dizziness** | **Calendar-Driven** | **Toxicity** |
| **Encephalopathy** | **Event-Driven** | **Adverse Event Form** |
| **Headache** | **Calendar-Driven** | **Toxicity** |
| **Insomnia** | **Calendar-Driven** | **Toxicity** |

| Adverse Event | Collection Type | Collection Form[1] |
|---|---|---|
| **Neuropathy** | **Event-Driven** | **Adverse Event Form** |
| **Reversible posterior leukoencephalopathy syndrome (PRES)** | **Event-Driven** | **Adverse Event Form** |
| **Seizure** | **Event-Driven** | **Adverse Event Form** |
| **Severe muscle weakness/paralysis** | **Event-Driven** | **Adverse Event Form** |
| **Somnolence** | **Calendar-Driven** | **Toxicity** |
| **Syncope (fainting)** | **Calendar-Driven** | **Toxicity** |
| **OCULAR/VISUAL DISORDERS** | | |
| **Blurred vision** | **Calendar-Driven** | **Toxicity** |
| **Conjunctivitis** | **Calendar-Driven** | **Toxicity** |
| **Sudden loss of vision** | **Event-Driven** | **Adverse Event Form** |
| **RENAL DISORDERS** | | |
| **Cystitis Non-infective** | **Calendar-Driven** | **Toxicity** |
| **Acute kidney injury** | **Calendar-Driven** | **Toxicity** |
| **Chronic kidney disease** | **Calendar-Driven** | **Toxicity** |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | | |
| **Bronchitis** | **Calendar-Driven** | **Infection** |
| **Cough** | **Calendar-Driven** | **Toxicity** |
| **Dyspnea** | **Calendar-Driven** | **Toxicity** |
| **Hypoxia** | **Calendar-Driven** | **Toxicity** |
| **Pleural effusion** | **Calendar-Driven** | **Toxicity** |
| **Pneumonia** | **Calendar-Driven** | **Infection** |
| **Sinusitis** | **Calendar-Driven** | **Toxicity** |
| **Sore throat** | **Calendar-Driven** | **Toxicity** |
| **SKIN AND SUBCUTANEOUS TISSUE DISORDERS** | | |
| **Pruritis** | **Calendar-Driven** | **Toxicity** |
| **Rash** | **Calendar-Driven** | **Toxicity** |
| **Hyperhidrosis (excessive sweating)** | **Calendar-Driven** | **Toxicity** |
| **VASCULAR DISORDERS** | | |
| **Capillary leak syndrome** | **Calendar-Driven** | **Toxicity** |
| **Thromboembolic event** | **Calendar-Driven** | **Toxicity** |
| **OTHER** | | |
| **Pregnancy** | **Event-Driven** | **Adverse Event Form** |
| **Second primary malignancy** | **Event-Driven** | **Adverse Event Form** |
| **Other unexpected grade 3-5 AE** | **Event-Driven** | **Adverse Event Form** |

[1]Events determined to be at least possibly related to bortezomib that occur more than 30 days from the last dose may be reported via the Bortezomib SAE Screening Form and Adverse Event Form at the discretion of the investigator.

## I.7 Adverse Event Reporting POST Randomization:

This section outlines the reporting requirements for patients who are randomized. All randomized patients must adhere to each required level of event reporting as outlined in this section.

### 1.7.1 Reporting Serious Adverse Events During Maintenance Therapy

The following section outlines adverse event reporting requirements for patients beginning with the first dose of maintenance therapy until 30 days after the final dose of maintenance therapy.

**All serious adverse events that meet the SAE criteria outlined in I.1 above will require reporting through the event-driven AE mechanism in Advantage EDC from the first dose of maintenance therapy through 30 days after the last dose of maintenance therapy and regardless of relationship.**

**Post-randomization period AE data collection:**

- **Re-Admission/Hospitalization Form**: this form documents all hospital admissions that occur after randomization. Any hospitalizations that occur from the first dose until 30 days from last dose of maintenance will also require submission of the Adverse Event Forms.
- **Infection Form**: this form documents infections that occur after randomization. If the infection fulfills the SAE definition and occurs from the first dose until 30 days after the last dose of maintenance, the Adverse Event Forms will be required.
- **Death Form**: this form documents the death of a patient. If death is associated with an adverse event and it occurs from the first dose through 30 days after the last dose of maintenance, the Adverse Event Forms will be required.
- **Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, regardless of attribution to any of the study interventions. These forms are also used to collect information on any SAE event from the first dose of maintenance therapy through 30 days after the last dose by the additional adverse event reporting requirements. These events require expedited reporting and will be reviewed by the Medical Monitor at the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.

# APPENDIX J

# DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

**Background – The Sequential Probability Ratio Test**

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0:\theta=\theta_o$ versus $H_1:\theta=\theta_1$ decides in favor of $H_1$ or $H_0$ if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1)/f(x_i;\theta_0)$ is the likelihood ratio, and $c_\alpha$ is determined to have the size $\alpha$. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B<1<A$, stops sampling and decides in favor of $H_1$ as soon as $L_n > A$, and stops sampling and decides in favor of $H_0$ as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities $\alpha$ and $\beta$ of rejecting $H_0$ when $\theta=\theta_0$, and of accepting $H_0$ when $\theta=\theta_1$, respectively, and the expected sample size $E(N\mid\theta_j)\equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0)\le\alpha$ and $\Pr_1(\text{reject } H_0)\le\beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities $\alpha$ and $\beta$ minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2, \ldots$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing $\theta_0$ against $\theta_1(>\theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities $\alpha$ and $\beta$, the SPRT boundaries are given approximately by $A=(1-\beta)/\alpha$ and $B=\beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1)=(A^{h(\theta)}-1)/(A^{h(\theta)}-B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int(f(x;\theta_1)/f(x,\theta_2))^{h(\theta)} f(x;\theta)dx=1$.

The formula $E(N;\theta)=[[1-O(\theta)]\log A+O(\theta)\log B]/E(z;\theta)$ provides the average sample number for an arbitrary $\theta$. The sample size distribution is very highly skewed, $Var(N)\approx[E(N)]^2$. Thus we will consider a truncated test with maximum sample size of $N_0$ and simulate to obtain the operating characteristics of the test.

**Derivation of the SPRT for Censored Exponential Survival Times**

Suppose that we wish to construct a sequential test for the composite null hypothesis that the rate of overall mortality at an early time point t is less than or equal to $p_0$ versus the alternative hypothesis that it is greater than or equal to $p_0$. Let us assume that the survival times, $T_1, T_2, ..., T_n$, are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. Although an exponential model may not fit well for overall mortality, it usually provides a reasonable model over a short time frame for modeling toxicity, so in all discussion below we assume that exponential survival times are censored at time point t. In the exponential parameterization, a t-day survival rate of $p_0$ translates into a mean survival of $\mu_0$=-t/ln(1-$p_0$) (rate parameter $\theta_0$ = -ln(1-$p_0$)/t). .

The SPRT is derived with reference to a simple null and alternative hypothesis for the rate parameter, in this case, $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$. The log-likelihood ratio for the exponential in the presence of censoring is $\log \prod_i^n f(x_i;\theta_1) - \log \prod_i^n f(x_i,\theta_0) = d(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, where d is the number of events. The SPRT can be represented graphically when plotting the number of deaths (d) on the y axis against the total time on study $\sum_i^n T_i$ on the x axis. The continuation region in terms of d is bounded by two parallel lines given by

$$\left[\frac{\log(B)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i < d < \left[\frac{\log(A)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i$$

with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0)$, and intercepts $\log A/(\ln\theta_1 - \ln\theta_0)$ and $\log B/(\ln\theta_1 - \ln\theta_0)$, for the upper and lower bounds, respectively. For monitoring purposes, at an interim analysis calendar time point s, suppose that d(s) events have occurred and that the total time on study is $\sum_i^n T_i(s)$.The cumulative number of events d(s) is plotted on the y axis against the total time on study, $\sum_i^n T_i(s)$. When this graph crosses the upper boundary, the null hypothesis is rejected. In practice, monitoring will be scheduled monthly after the start of enrollment to the study.

A truncated version of the SPRT can be obtained by specifying a maximum sample size. We truncate the SPRT by declaring that if the test has failed to terminate after the maximum sample size, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at the maximum sample size is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity. The operating characteristics of this proposed truncated SPRT for censored exponential data can be estimated by simulation.

# APPENDIX K
# PRODUCT COMPLAINTS FOR BORTEZOMIB AND IXAZOMIB

## PRODUCT COMPLAINTS FOR BORTEZOMIB AND IXAZOMIB

A product complaint is a verbal, written, or electronic expression which 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 Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.

**For product complaints, contact:**
**Phone: 1-844-ONC-TKDA (1-844-662-8532)**
**E-mail: GlobalOncologyMedinfo@takeda.com**
**FAX: 1-800-881-6092**
**Hours: Mon-Fri, 9 a.m. – 7 p.m. ET**

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, then the appropriate forms in AdvantageEDC should be completed (refer to Section 4.7 Adverse Event Reporting).

# APPENDIX L
# MINIMAL RESIDUAL DISEASE ANCILLARY STUDY

# BMT CTN 1302 Ancillary Study
# Assessment of minimal residual disease (MRD) and immune reconstitution by flow cytometry to analyze the efficacy and immune-related effects of ixazomib maintenance post-allogeneic BMT

## 1.0. Objectives:

### 1.1. To determine the level of minimal residual disease (MRD) using a comprehensive immunophenotyping panel before alloBMT, before starting maintenance ixazomib/placebo and at 18 months after alloBMT.

**1.1.1.** Estimate the rate of conversion from detectable to undetectable minimal residual disease with alloBMT (at time of staging D+60 to 120).

**1.1.2.** Compare the rate of conversion from detectable to undetectable minimal residual disease between time of randomization between ixazomib maintenance vs placebo and 18 months post-alloBMT.

### 1.2. To describe the changes in immune cell subpopulations using a comprehensive immune reconstitution panel before alloBMT, before starting maintenance ixazomib/placebo and at one year after alloBMT.

**1.2.1.** Explore the relationship of immune cell populations with development of acute and/or chronic GVHD.

**1.2.2.** Explore the relationship of immune cell populations with MM disease staging and PFS.

**1.2.3.** Explore the relationship of immune cell populations with TRM and OS.

## 2.0. Preliminary Data and Background:

There is increasing evidence of the role of the immune system in controlling and/or eradicating minimal residual disease (MRD) in multiple myeloma (MM). Novel agents, combined with allogeneic BMT, have the potential to be harnessed to accomplish long-term disease control and perhaps a cure for MM. Studying the role of immune cell subsets in relation to detection of MRD and long-term PFS may improve our understanding of myeloma cell biology and the immune cell subsets that are potent myeloma cell-killers.

We are currently measuring MRD as a NIH-funded ancillary study to BMT CTN 0702 (PRIMeR study). The parent trial (STaMINA) recently closed to accrual. The first specific aim of the PRIMeR study is to assess the correlation of MRD with traditional MM staging (SPEP, SIFE, UPEP, UIFE, sFLC ratio). The analysis of baseline/pre-autologous BMT samples and staging should be ready to start in the spring 2014. These initial analyses will help guide and refine the immunophenotyping panel for MRD which is proposed in this study. Having the same flow cytometry laboratory perform and analyze the MRD for both the 0702 and 1302 trials will insure consistency and the ability to draw inferences between the 2 treatment strategies (auto/allo BMT). We recently presented preliminary data at ASH 2013 of immune cell subpopulations before and after autologous BMT for MM. Several immune cell subsets were strongly correlated with early

absolute lymphocyte (ALC) recovery, as well as PFS and OS. Our analysis demonstrated, however, that these immune cell subsets were independent of traditional MM staging, and therefore convey information in addition to MRD. We propose that in the alloBMT setting, the immune cell profiles of MM patients will be even more meaningful and may predict additional outcomes, such as acute and chronic GVHD, and may help guide future treatments to manipulate the immune system to eradicate residual myeloma post-alloBMT. The BMT CTN 1302 trial provides a unique opportunity to study the role of ixazomib maintenance post-alloBMT in immune surveillance/eradication of MRD in MM.

## 3.0. Study eligibility:

All 138 patients enrolled on BMT CTN 1302 are eligible.

## 4.0. Outcomes:

The results of this ancillary study can provide preliminary data of the ability of ixazomib vs placebo to eradicate MRD in myeloma patients post-alloBMT. In addition, we will generate preliminary data evaluating the impact of immune cell subsets on the efficacy of ixazomib, their association with acute and chronic GVHD, and overall prognosis (PFS/OS) which will provide critical information on potential ways the immune system may be harnessed in future studies to improve patient outcomes after alloBMT for myeloma.

Future exploratory analyses could compare the impact of autoBMT (BMT CTN 0702) vs alloBMT (BMT CTN 1302) on clearance of MRD as well as the prognostic impact of MRD positivity by immunophenotyping on long-term PFS and OS.

## 5.0. Summary of methods:

Currently, we have the capability to perform up to 10-color flow panels in a CLIA accredited clinical flow cytometry laboratory. This will allow the following panels to be run:
CD38/LD/CD45/CD56/CD138/CD19/CD20/CD81
CD38/LD/CD45/ CD28/ CD138/CD27/CD19/CD117
CD38/LD/CD45/cLambda/CD138/CD19/cKappa

For detection of minimal residual disease (myeloma) (recommended in Rawstron et al, 2008) and under consideration by the NIH/FDA Detection of Myeloma MRD consensus committee (PKW personal communication):

Our preliminary analysis of MRD in BMT CTN 0702 (STaMINA/PRIMeR) will determine the best gating strategy and the importance of measuring cytoplasmic light chain expression. Data will be analyzed per our standard methodology, using a common series of macros and templates and scored on a sample-by-sample basis for each of these parameters. A minimum of $2x10^6$ events are acquired with a sensitivity of less than 0.01%. These mAb combinations make a sensitive and specific panel for detection of MRD. However the acquisition, analysis and interpretation adds

complexity to the analysis and may impact wide-spread reproducibility in some centers with limited flow cytometric capabilities.

For immune reconstitution/immune cell subpopulations:

| **Cell Subsets** | **Antibody Pannels** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Inflammatory Monocytes &DC** | CD11c | CD123 | DUMP | HLADR | CD14 | CD45 | CD163 | CD16 |
| **RTE, CD4 & CD8 Naïve & Memory** | CD31 | CD28 | CD8 | CD3 | CD45RA | CD4 | CCR7 | CD45RO |
| **Tregs (1)** | CD25 | CD39 | CD73 | CD3 | CD178 | CD45RA | CD127 | CD4 |
| **NKs (1)** | CD57 | CD314 | CD16 | CD3 | CD159a | CD45 | CD33 | CD56 |
| **γd T Cells** | V Delta 1 | V Delta 2 | CD8 | CD3 | αβ TCR | CD45 | CD25 | γd TCR |
| **B Cells** | IgM | CD319 | IgD | CD19 | CD27 | CD45 | CD138 | CD38 |

Time points of Sample collection

Bone marrow aspirate will be used for the MRD assessment collected at three timepoints: prior to transplant, prior to initiation of maintenance and one month after completion of maintenance. According to the experience of previous clinical trials with the rate of agreement in providing bone marrow aspirates for research purposes, and the proportion of patients having a marrow performed to confirm complete response, we estimate that we will obtain 120 samples at baseline, 50 samples prior to initiation of maintenance, and 30 samples upon completion of maintenance.

Peripheral blood for immunereconstitutional assays will be collected prior to initiation of maintenance, at the start of cycle 5 of maintenance and one month after completion of maintenance. The numbers of peripheral blood samples estimated at each timepoint are 100 samples prior to maintenance, 65 at cycle 5, and 50 at completion of maintenance.

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# APPENDIX M
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