



## FAQs for BMT CTN PROTOCOL 1302

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

#### **1. Why run a trial to evaluate allogeneic transplant in multiple myeloma?**

Allogeneic hematopoietic cell transplantation (HCT) is considered the only curative option for patients with multiple myeloma (MM), but due to previously perceived higher toxicities its role has remained investigational. Although the overall survival of myeloma patients improved with the advent of novel agents, high-risk MM continues to pose a significant therapeutic challenge with shortened survival.<sup>1</sup> Several recent single center experiences demonstrated promising activity of allogeneic HCT in MM resulting in increasing interests in incorporating novel agents to allogeneic HCT platform<sup>2-4</sup>. Relapse following HCT is a major reason for treatment failure and maintenance therapy with novel agents may improve the outcome of allogeneic HCT. Therefore, we designed a clinical trial to examine the role of allogeneic HCT in high-risk MM to address this unmet medical need.

#### **2. How was the patient eligibility related to characteristics of multiple myeloma defined?**

The criteria for eligibility have been chosen to include patients with MM that have the highest risk of progression and shortest overall survival. Also these criteria have been carefully chosen to ensure that within this high risk group, only those with an expected benefit to allogeneic transplantation are eligible.

With these considerations in mind, we have two broad categories of patients who will be eligible, according to history of prior disease progression.

- Patients with very high risk MM as defined by high risk chromosomal, FISH or gene expression abnormalities (e.g, karyotypic del 13, chr 1 abnormalities, loss of p53/del 17p) are eligible if in partial response or better disease control. Patients with plasma cell leukemia are also in this category however they need to be in a very good partial remission (VGPR) or better to be eligible.<sup>5</sup> In general, these patients have an expected progression free survival of <18 mo from diagnosis with current approaches including novel agent based therapies, multi agent chemotherapy and autologous transplantation<sup>6-8</sup>.
- The next eligibility category includes patients who experienced no more than one prior disease progression. These patients are eligible if they progress within 18 months after an autologous HCT and achieve VGPR or better prior to enrollment. Patients without a prior autologous transplant would be eligible if they fulfill criteria of high risk disease as above, experience disease progression from 18 months from initiating anti-myeloma therapy and achieve a VGPR or better prior to enrollment. The table below summarizes the eligibility according to disease risk.

Disease	Disease Status	Prior Progression	Prior Therapy/Auto HCT
High Risk <sup>1</sup> Multiple Myeloma	≥ PR	None	within 18 months from initiation of systemic anti-myeloma therapy which may include single or planned tandem autologous transplant
Plasma Cell Leukemia	≥ VGPR	None	within 18 months from initiation of systemic anti-myeloma therapy which may include single or planned tandem autologous transplant
Standard Risk Multiple Myeloma	≥ VGPR	1	progression or relapse within 18 months from an autologous HCT which may include single or planned tandem
High Risk <sup>1</sup> Multiple Myeloma	≥ VGPR	≤ 1	progression or relapse within 18 months from initiation of systemic anti-myeloma therapy but NO prior AutoHCT

### 3. How is the inclusion of a heterogeneous cohort of patients with and without prior disease progression being addressed in this clinical trial?

MM is a heterogeneous disease and outcome of patients can vary from a smoldering state to a rapidly progressive disease and short survival. The current definition of high risk MM requires assessment of chromosome abnormalities, markers of plasma cell proliferation, circulating plasma cells and more recently gene expression profiles. Patients that present these features are considered to be of high risk given shorter time to progression and overall survival. However other patients who lack these disease characteristics may also have shorter time to progression. For these patients time to progression is an important risk determinant. This trial targets a population with expected worse outcomes due to upfront features and timing to second therapy.

However we do recognize that the eligibility criteria are unusual and it may result in unbalanced enrollment. Thus, the study will be stratified according to prior disease progression. We anticipate that patients with prior to disease progression will account for a larger subset of patients being enrolled in this trial.

### 4. What are the interventions being tested in this protocol?

The current protocol examines two interventions, a reduced-intensity conditioning regimen for allogeneic HCT and a maintenance strategy. The conditioning regimen consists of fludarabine (30 mg/m<sup>2</sup>/day intravenously on Days -5 to -2), melphalan (70 mg/m<sup>2</sup>/day on Days -3 and -2) and bortezomib (given before and after HCT) which is derived from a single center study with a 2-year non-relapse mortality of 17% in upfront allogeneic HCT setting.<sup>4</sup> Bortezomib has also been evaluated as graft-versus-host disease (GVHD) prevention in phase I/II studies where bortezomib given on Days +1, +4, and +7 resulted in reduction of acute GVHD.<sup>9,10</sup> Post-HCT bortezomib will be given in combination with standard tacrolimus plus methotrexate GVHD prevention (similar to BMT CTN 1203). The suitable donors are either related or unrelated adults who are HLA-matched (8/8) at HLA-A, -B, -C and -DRB1 loci.

<sup>1</sup> High Risk: 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; high risk criteria based on GEP; or Beta-2M ≥ 5.5 mg/L.

Maintenance therapy will initiate between Day +60 and +120 after allogeneic HCT. Patients will be randomized to either oral ixazomib maintenance or placebo. Ixazomib, a novel oral proteasome inhibitor, will be administered for a maximum of 12 cycles. Starting dose of ixazomib is 3 mg orally given on Days 1, 8, and 15 on a 28-day cycle. If patients are able to tolerate ixazomib without significant toxicity, the dose of ixazomib will be increased to 4 mg after 3 cycles of therapy. Dosing adjustment guidelines are incorporated in order to adjust maintenance therapy based on toxicity.

### **5. Why was ixazomib selected as a maintenance therapy?**

Ixazomib is an orally bioavailable, boronic acid containing, and reversible proteasome inhibitor. It appears to be different from its precursor agent bortezomib in terms of enzyme inhibition characteristics and side effects. Notably it retains the efficacy against myeloma<sup>11</sup> while having a better tolerated oral dosing schedule either once weekly or twice weekly. Neuropathy rates as published have been lower and the drug itself is in a regulatory approval pathway. Most major investigators in MM have experience with the drug in clinical trials.

In addition to the favorable efficacy, toxicity profile and dosing schedule, we considered the additional advantages of proteasome inhibitors in genetically defined high risk disease with proteasome inhibitor therapy as maintenance. This concept has been tested in the HOVON 65 trial<sup>7</sup> with Velcade maintenance after autologous transplants and found to be especially effective. In the allograft setting promising phase II data has emerged from Kroger et al with Bortezomib post transplant to enhance remission and maintain disease control without risking GVHD<sup>12</sup>. Thus we believe proteasome inhibition is the ideal maintenance strategy.

In addition, immunomodulatory based maintenance runs the possibility of inducing graft-vs.-host disease which would be detrimental and makes maintenance infeasible.<sup>13</sup> Thus Ixazomib was chosen for its favorable safety, efficacy, dosing schedule attributes and with biologic targeting of high risk disease in mind.

### **6. Why not do a straight phase II trial with an allogeneic transplant followed by maintenance?**

Currently maintenance therapy is not the standard of care after allogeneic HCT for multiple myeloma. While the results of maintenance therapy with lenalidomide after autologous stem cell transplant have shown prolongation of progression-free and overall survival;<sup>14</sup> such results have not been demonstrated after allogeneic HCT. The results of HOVON76 trial showed that post-transplant maintenance therapy with lenalidomide might exacerbate the graft-versus-host disease<sup>15</sup>. Furthermore, the tolerability of additional therapy immediately after allogeneic transplantation is also a concern. It was thus felt necessary to conduct a randomized trial comparing placebo versus Ixazomib to establish the feasibility and efficacy of post-allotransplant maintenance therapy.

### **7. How are the investigators handling the development of GVHD after initiation of maintenance?**

For the initiation of maintenance therapy and for the initiation of a new cycle of therapy, patients are allowed to have grade 1-2 skin acute GVHD but no visceral (gut and liver) acute GVHD. Patients will be seen weekly during cycle 1 and cycle 4 (after the dose is increased) for monitoring of their symptoms. Patients will continue to be followed by the investigators on a monthly basis during the maintenance therapy. If a patient develops grade 3-4 acute GVHD or severe chronic GVHD, then the study drug will be discontinued. For grade 1 to 2 acute GVHD and mild to moderate chronic GVHD, the study drug will be continued. If a patient requires chronic GVHD therapy in addition to steroids and calcineurin

inhibitor(s), then the study drug will be discontinued. Management of GVHD will be conducted per institutional guidelines. Of note, the protocol recommends to initiate immunosuppression taper after Day +90 in the absence of GVHD.

### **8. Is this trial feasible?**

We firmly believe the trial is feasible for the following reasons:

1. High risk MM patients with an early relapse following autografts form a group for which all current therapies are suboptimal. Approximately 20-25% of autologous transplant recipients will relapse within 2 years. A subset of these patients (based on age, performance status, effectiveness of second line therapy, proximity to allogeneic transplant center) will be eligible for a second transplant. Since there are >6000 autologous transplant performed in the US, we expect this cohort to be at least 500 patients annually. We will establish outreach with major transplant centers to consider the BMT CTN 1302 trial for these patients.
2. High risk patients identified at diagnosis (by genetic tests) comprise 20% of all patients and this trial is appropriate for them too. However with competing non transplant trials and late transplant options we expect about 30-40% of this cohort to be offered this trial. Most centers in the BMT CTN who participated in the recently accrued BTN CTN 0702 trial will participate on the 1302 trial too. There were 750 patients enrolled in the 0702 trial and 20% of all MM patients have high risk disease, thus we would expect to have at least 50 patients per year available for this trial at the same centers.
3. High risk patients enrolled in alternative non transplant trials would also be eligible for the 1302 trial at progression. Therefore we do not consider such trials to be directly competing.
4. Patients who are being followed at major BMT CTN centers on the BMT CTN 0702 MM trial will be eligible if they have an early relapse.
5. A feasibility survey completed by the protocol team identified 29 who have expressed interest and willingness to participate.
6. A common issue with allogeneic HCT for myeloma is lack of insurance coverage except on national multicenter clinical trials and we expect the availability of a trial to boost insurance approvals.
7. In current environment, even without multicenter trials and the availability of only non-transplant trials, approximately 100 allogeneic transplants are performed annually in the US. We expect these numbers to increase when the trial opens. Most of the current allogeneic activity in MM happens at 5- 7 major centers all of whom are represented on the protocol team.

### **9. Why are patients being randomized prior to maintenance?**

This study is designed to assess both the effects of allogeneic transplant in high risk myeloma patients as well as the effect of maintenance post-allogeneic transplant. All patients will receive an allogeneic HCT and subsequently maintenance with ixazomib will be evaluated. The protocol team discussed the possibility of pre transplant randomization but elected to randomize close to the intervention of interest. This approach will enrich the number of patients receiving maintenance in the analysis. Patients who enrolled in the study and do not reach maintenance will be equally split between the arms for the analysis. Progression free survival will be calculated from maintenance and from transplant. The latter will use a reverse weight estimator to account for patients who do not reach maintenance.

### **10. Why is the primary end point time to progression?**

The primary outcome measure for a study should be a measure that is both objective and clinically relevant while allowing for identification of clinically significant effects or improvements in subject outcomes. Additionally, the period of assessment must be long enough to observe various aspects (both positive and negative) of the therapies but not so long as to delay reporting of meaningful results. The primary question for this study is the effect of maintenance therapy in improving patient outcomes following allogeneic transplant. Time to progression or death from randomization will be compared among patients achieving randomization. This is a clinically relevant endpoint and which will inform and influence current practice as well as provide important information for future studies.

**11. Accrual Estimates:** *please see separate document*

**References**

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