



## **IMPORTANCE OF THE QUESTIONS BEING ADDRESSED**

### **FAQs for BMT CTN 0702 LONG TERM PROTOCOL**

#### **1. Why implement a long term follow up for BMT CTN 0702?**

The BMT CTN 0702 was designed to include a fixed length of maintenance in all three arms. During protocol development, the results of CALGB/ECOG 100104 showing survival advantages with lenalidomide maintenance were not known<sup>1</sup>. Also, the BMT CTN felt that prolonging the intervention to an indefinite point would not be logistically feasible. However, as the data on lenalidomide maintenance matured, two studies demonstrating survival advantage with this approached included maintenance until disease progression<sup>1,2</sup>. One study demonstrating time to progression advantage but no survival advantage was limited to two years of maintenance<sup>3</sup>. As this data became available, physicians and patients enrolled to the BMT CTN 0702 inquired what to do after they complete three years of maintenance. Many patients and physicians expressed the desire to continue on commercial lenalidomide when they complete study drug. The idea of expanding the access of lenalidomide to patients willing to continue was entertained by the protocol team. Several approaches were discussed. First option was to amend the protocol and alter the length of maintenance from three years to until disease progression. This approach was felt to be problematic because it would require re-consenting all patients on study, which would not affect some patients who eventually meet the primary end point of the trial before the 3 year of maintenance was reached. Additionally, patients who were against this approach and did not consent the protocol amendment would be considered off study treatment. Thus, amending the protocol would result in excess work for participating sites and would risk reducing the number of patients evaluable for the primary endpoint. Second option was to develop an expanded access protocol to provide lenalidomide to only patients who have not progressed after three years of maintenance and who agree to continue study drug. This approach would allow consenting patients who were about to complete maintenance and would not affect the primary endpoint of the parent trial. However, following only a subset of patients could be unbalanced across the three arms, could theoretically affect any long term outcome analysis by treatment arm according to the initial randomization. Additionally, ascertainment bias for those in the expanded access versus those not would be difficult to correct. Thus, the protocol team decided on following all patients regardless of whether lenalidomide maintenance was completed. It would allow us to extend the follow up and perform a more formal long term outcomes analysis, evaluate the incidence of second primary malignancies, and continue to collect health quality of life information.

#### **2. How does the implementation of this protocol affect the parent trial?**

The statistical analysis plan indeed overlaps with the implementation of the long term follow up protocol. The primary endpoint for the parent trial is progression free survival evaluated as time to event in different time points starting at 1 year after the last enrolled patient through 4 years after the last enrolled patient. Due to the differential length of interventions across the three arms of the parent trial, patients

will be on therapy for 3 years and 2 months, 3 years and 4 months and 3 years and 6 months for the autologous hematopoietic cell transplant (autoHCT) followed by maintenance, tandem autoHCT followed by maintenance, and autoHCT followed by consolidation and maintenance, respectively. In fact, according to allowable times in between interventions, some patients might complete maintenance by 4 years from study entry. Thus, enrollment to the long term follow up would be different depending on the treatment arm. The selected approach to address this overlap is to censor the analysis of the primary endpoint of the trial to 3 years and 2 months, this will allow performing the analysis for patients at the same time from randomization and all patients will be on therapy. We are confident that by modifying the statistical plan of the parent trial will resolve the potential overlap between the two protocols.

### **3. What happens if patients do not want to continue lenalidomide maintenance?**

All patients will be followed in the long term follow up protocol. There is a concern of treatment fatigue or fatigue related to frequent evaluations in a clinical trial. The Long Term Follow up protocol has less frequent schedule of events, including twice a year follow up assessment. Capture of adverse events will be the same as the parent trial. Some patients will elect not to participate in the long term follow up. These patients will complete their follow up on BMT CTN 0702 and will be censored at 3 years and 2 month-time point for the long term follow up analysis. Data from the CIBMTR will be utilized for long term follow up on these patients.

### **4. Are all patients in the BMT CTN 0702 eligible to continue maintenance in the the Long Term Follow up protocol?**

Yes, all patients who completed 3 years of maintenance and who have not experience disease progression are eligible for the Long Term Follow up protocol. During the implementation phase of this protocol, there will be a gap whereby patients are completing maintenance and the Long Term Follow up protocol is not available. Participating centers will receive a memo announcing the plans and development of the Long Term Follow up protocol once it is approved by the NHLBI PRC. Patients who complete three years of maintenance can stop maintenance and wait for activation of the long term follow up protocol or they can initiate commercial drug on their own insurance expenses at the same maintenance dose until enrollment in the Long Term Follow up protocol at the discretion of the treating physician. All patients will be eligible regardless of the time off lenalidomide maintenance between successful completion of the parent trial maintenance period and enrollment in the Long Term Follow up protocol, as long as there is no clinical evidence of disease progression.

### **5. Why use progression free survival as the primary endpoint of the Long Term Follow up protocol?**

Long term outcomes are critical in myeloma trials. Several trials demonstrated differences between interventions after 3 or even 5 years of follow up. Keeping the Long Term Follow up protocol in line with the parent trial will strengthen subsequent analyses of the parent trial. The Long Term Follow up protocol will allow us to have a formal structure for analyzing PFS along with other endpoints of interest such as second primary malignancies, adverse events, and health related quality of life.

## **6. Why are second primary malignancies (SPM) included in this protocol?**

The development of SPMs was an important finding of the two first trials that evaluated lenalidomide maintenance after autoHCT<sup>1,2,4</sup>. This association was identified during the initial phases of accrual to the BMT CTN 0702 which resulted in an amendment to the informed consent and all patients were required to re-consent to the clinical trial. The French trial limited the maintenance duration when this association was observed. In the US, the NCI CTEP issued recommendations for active monitoring the patients who were on trial, but did not recommend maintenance to be stopped. In fact, a post hoc analysis in the CALGB/ECOG 100104 trial including SPMs in an event-free survival composite endpoint including progression and death, demonstrated that the advantages with lenalidomide maintenance over placebo persisted. The parent trial does not include SPMs as a separate endpoint. We included in the Long Term Follow up protocol this endpoint as further understanding of this risk is important to advance the field.

## **7. Why is the study duration planned until the end of 2018?**

The logistic issues of having a trial open without an end date remains a problem. The NHLBI recommended the network to avoid trials that may outlast the existence of the network. The current funding cycle for the BMT CTN will be completed in 2017. This protocol as it stands will continue until 2018. If the BMT CTN continues, an amendment will be required. Conversely if the BMT CTN ceases to exist, the protocol team will need to create a new structure to continue to provide drug and follow up.

## **8. What is the value of this protocol?**

This protocol offers access to study drug to patients so maintenance can be continued until disease progression. This approach is in line with current data that of survival benefit of lenalidomide maintenance after autoHCT. Additionally, this protocol will provide a structure for formal evaluation of the long term outcomes including the development of SPMs. This protocol gives an opportunity to assess the impact of long term maintenance therapy on QOL and also to further understand the compliance of these prolonged interventions.

## **9. Accrual estimates – See separate Summary of Anticipated Accrual Report**

### **References**

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<sup>1</sup> McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.

<sup>2</sup> Palumbo A, Gay F, Spencer A, et al. A Phase III Study Of ASCT Vs Cyclophosphamide-Lenalidomide-Dexamethasone and Lenalidomide-Prednisone Maintenance Vs Lenalidomide Alone In Newly Diagnosed Myeloma Patients. *Blood*. 2013;122:763.

<sup>3</sup> Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782-1791.

<sup>4</sup> Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol*. 2014;15:333-342.