IMPORTANCE OF THE QUESTIONS BEING ADDRESSED
FAQs for BMT CTN PROTOCOL 0702

1. Why conduct a transplant trial in multiple myeloma?

Autologous hematopoietic cell transplantation (HCT) prolongs progression free and overall survival of patients with multiple myeloma (MM) and thus remains a standard treatment approach for this disease. Despite being the most common indication for autologous HCT in the U.S.[1] MM remains an incurable illness. Several new agents such as lenalidomide and bortezomib have been approved for treatment of MM and despite their high response rates, are not curative. Hence, combining autologous HCT with these novel agents may further improve progression free and overall survival. However, the question of how to best incorporate these therapies into a transplant regimen remains unanswered.

2. Why have tandem autologous transplants as the control arm?

Since the publication by Attal et al,[2] high dose therapy and autologous HCT is recognized as the best available therapy for newly diagnosed patients with MM. Two studies, both randomized trials, analyzed on an intention to treat basis, demonstrated superior outcome for patients receiving tandem vs. single autologous HCT.[3, 4] The French IFM94 study demonstrated a 7-year event-free survival (EFS) of 10% in the single transplant group compared to 21% in the tandem autologous group. A subgroup post hoc analysis showed that the greatest benefit to tandem transplant was seen in the group who did not achieve a complete remission or very good partial remission (CR or VGPR) after the first transplant. This suggests that part of the benefit of the tandem approach was in upgrading the response.[4] The Bologna 96 trial demonstrated that tandem autologous HCT significantly increased the probability of attaining a CR plus near CR (47 vs 33%) and prolonging EFS (35 vs 23 months) compared to a single autologous HCT. Administration of novel agents after disease relapse or progression in the single autologous HCT arm was felt to contribute to the similar overall survival (OS) between the arms.[3]

It is unknown whether an alternate approach such as planned intensive consolidation therapy after one autologous HCT combined with subsequent maintenance therapy will provide the same or superior PFS and OS to tandem autologous HCT. The Bologna 96 experience with use of novel agents at relapse post transplant, suggests that they will have a role in improving OS. Hence, the BMT CTN #0702 trial will incorporate these agents in a planned fashion as consolidation and maintenance therapy.

3. Why include lenalidomide maintenance therapy?

The IFM 99-02 trial demonstrated that maintenance therapy with thalidomide improved OS (87% in the thalidomide arm vs. 77% in the no maintenance arm).[5] Patients received thalidomide for a median of 15 months, with drug related effects leading to discontinuation in 39%. The benefit of thalidomide was only in patients who did not have deletion 13. A Tunisian trial utilized 6 months of thalidomide after single

autologous versus tandem autologous HCT with no thalidomide.[6] The three year OS was superior in the thalidomide arm (85% vs. 65%). However, the OS in the tandem arm is significantly inferior to the Bologna 96 trial, and in contrast the 3 year OS in the thalidomide arm is superior to the single transplant arm in the IFM 94 and Bologna 96 trials.[3, 4] It is unknown whether such differences can be attributed to thalidomide alone. Also data on cytogenetics in this study population are unknown.

Lenalidomide as a maintenance therapy has a more favorable side effect profile than thalidomide, which may allow more prolonged use post-transplant. In addition, there is an ongoing CALGB trial (CALGB/ECOG #100104) that compares post transplant lenalidomide maintenance with placebo. Preliminary experience suggests that this treatment approach is well tolerated.[7] The BMT CTN #0702 trial will also allow the study of whether lenalidomide maintenance will benefit patients with deletion 13 who did not seem to derive the same benefit from thalidomide maintenance.

4 **Why did the protocol team select a three-year period for maintenance therapy?**

The optimal length of maintenance therapy is largely unknown. Some studies keep patients on maintenance until evidence of disease progression or relapse (CALGB #100104).[5, 8] The BMT CTN multiple myeloma trial (#0102) included maintenance with thalidomide and dexamethasone for one year in patients who were assigned to a tandem autologous HCT. The protocol team chose a three-year maintenance period given the median progression-free survival of patients with MM being approximately three years. Also establishing a fixed period for maintenance improved the feasibility of this clinical trial, both in terms of the costs of provision and distribution of drug as well as in the patient follow-up required.

5. Why test the consolidation of bortezomib/lenalidomide/dexamethasone?

This combination therapy has been demonstrated to be highly effective in relapsed/refractory MM, with response rates of up to 79% and CR/nCR rates of 33% reported.[9] Additionally there is evidence that molecular responses can be achieved with a post autologous transplant consolidation approach.[10] The VRD regimen is now being used in the upfront setting and in as consolidation following induction therapy as part of an ECOG clinical trial. The doses and schedule of VRD in the BMT CTN #0702 trial are the same as in the ECOG trial. Given the high response rates, it can be anticipated that the use of this regimen as consolidation may lead to superior PFS compared to tandem transplant.

6. Why not develop a transplant versus no-transplant clinical trial for multiple myeloma?

The availability of new drugs in MM in combination with older anti-myeloma drugs lead to the development of numerous new regimens. Currently, it is unclear as to the optimal regimen for MM initial therapy. This clinical trial focuses on improving transplantation outcomes by adding novel anti myeloma agents post-transplant. Also logistically it would be difficult to design an induction trial from the transplant physician perspective, given the referral pattern most of these patients present to transplant centers after initiating or completing therapy.

7. Why consider a three-arm clinical trial?

All three arms are important in this trial and have the potential to change how autologous HCT is used in the setting of immunomodulatory drugs and proteasome inhibitors. The tandem autologous HCT in this trial is the control arm, similarly to the BMT CTN #0102. However, planned tandem autologous HCT are rarely performed outside the context of clinical trials in the U.S. Conversely, the single autologous HCT arm is the current standard of care and therefore inclusion of this arm plus maintenance therapy will improve the external validity of this trial. Finally, the consolidation arm is regarded as the investigative arm, to test whether this approach can abrogate the need for a second transplantation. Should this approach be validated, it will lead to a significant change in standard practice in the treatment of MM.

8. Why choose three-year progression-free survival as the primary endpoint?

The primary outcome measure for a study must incorporate in its measure both the potential positive and negative aspects of the therapy under study. Furthermore, its time point of assessment must be long enough to observe the positive and negative potentials of the therapies but not so long as to render the results moot by intervening developments. It must be an objective measure that is accepted as meaningful for the disease in question. For the questions under study: the role of consolidation therapy after autologous HCT compared to the role of tandem autologous HCT plus maintenance and autologous HCT followed by maintenance with a novel agent, three-year PFS meets this criteria. Response to either type of transplantation can take over a year to be fully realized as the death of non-clonogenic myeloma cells and the clearance of the myeloma protein is a gradual process. Maintenance therapy should result in a higher response rate during the first year, but it is not clear whether these responses will be maintained over time. Additionally, it is possible that increased responses will be offset by both early and late toxicities. In addition, the feasibility of administering four cycles of consolidation post transplant is unknown and it will be determined in this trial.

9. Is the study feasible?

As indicated at the outset, MM is now the most common indication for autologous HCT in the US. The BMT CTN #0102 enrolled 710 patients with MM over a period of 38 months, completing its accrual target as projected. Currently, even with the widespread use of novel agents, centers have not seen a large decrease in numbers of patients being referred for transplant. Despite these large numbers, individual centers do not see sufficient numbers of patients to allow this study to be conducted outside of a large network such as the BMT CTN. The participation of 15 BMT CTN Core Centers treating adult patients, active SWOG, ECOG and CALGB transplant programs and interested BMT CTN Affiliate Centers would be able to contribute with the accrual goal of 20 patients per month, which given past experiences with the BMT CTN #0102 and the CALGB #100104 is quite feasible. It is important to note, however, that the timing of this study is critical. There is at present significant interest in testing these strategies, but with delay, there is increasing potential for general implementation of these strategies by the transplant community without formal and definitive testing in a large comparative trial.

10. Accrual estimates – see separate Summary of Anticipated Accrual Report

REFERENCES

[1] Pasquini MC, Wang Z, Schneider L. Current use and outcome of hematopoietic stem cell transplantation: part I – CIBMTR Summary Slides, 2007. CIBMTR Newsletter [serial online] 2007;13(2):5-9.

[2] Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996 Jul 11;335(2):91-7.

[3] Cavo M, Tosi P, Zamagni E, Cellini C, Tacchetti P, Patriarca F, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007 Jun 10;25(17):2434-41

[4] Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003 Dec 25;349(26):2495-502.

[5] Attal M, Harousseau J-L, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance Treatment with Thalidomide after Autologous Transplantation for Myeloma: Final Analysis of a Prospective Randomized Study of the "Intergroupe Francophone du Myelome". ASH Annual Meeting Abstracts. 2005 November 16, 2005;106(11):1148-

[6] Abdelkefi A, Ladeb S, Torjman L, Othman TB, Lakhal A, Romdhane NB, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. Blood. 2008 February 15, 2008;111(4):1805-10.

[7] Philip McCarthy (CALGB/ECOG #100104 Principal Investigator) personal communication.

[8] Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med. 2006 Mar 9;354(10):1021-30.

[9] Richardson P, Jagannath S, Raje N, Jakubowiak A, Lonial S, Ghobrial I, et al. Lenalidomide, Bortezomib, and Dexamethasone (Rev/Vel/Dex) in Patients with Relapsed or Relapsed/Refractory Multiple Myeloma (MM): Preliminary Results of a Phase II Study. ASH Annual Meeting Abstracts. 2007 November 16, 2007;110(11):2714-.

[10] Ladetto M, Pagliano G, Avonto I, Santo L, Ferrero S, Cavallo F, et al. Consolidation with Bortezomib, Thalidomide and Dexamethasone Induces Molecular Remissions in Autografted Multiple Myeloma Patients. ASH Annual Meeting Abstracts. 2007 November 16, 2007;110(11):530-