BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

FAQs for BMT CTN Protocol 1902

Phase II Multicenter Trial of anti-B cell Maturation Antigen Chimeric Antigen Receptor T Cell Therapy for Multiple Myeloma Patients with Sub-Optimal Response After Autologous Hematopoietic Cell Transplantation and Maintenance Lenalidomide

1. Why run a Chimeric Antigen Receptor (CAR) T-cell study in first line of multiple myeloma (MM) therapy?

Over the last 25 years, the standard first line of myeloma therapy has been gradually intensified with stepwise improvements in overall survival demonstrated in multiple phase 3 studies. Transplant itself is one such intensification with proven overall survival benefit in multiple randomized studies. Likewise, addition of "imids" to induction, then imid/proteasome inhibitors (PI) combinations, and addition of lenalidomide maintenance have all improved overall survival[1,2]. As bb2121[3] (idecabtagene vicleucel or Ide-cel) and other anti-BCMA CAR T-cell products[4,5] have shown encouraging safety and efficacy in relapsed/refractory, it is logical to ask whether intensification of first-line therapy with CAR T-cells might similarly improve overall survival. Moreover, these prior CAR T-cell studies in MM suggest that most patients receiving CARs in the relapsed/refractory setting eventually relapse, highlighting need for approaches that might improve efficacy of CAR T-Cells. The 1902 study tests an approach incorporating CAR T-cells into first line MM therapy with the primary objectives of assessing safety/feasibility and secondary objectives of generating preliminary efficacy data that would be required to design further definitive studies. In addition, it is possible CAR T-cells would be more effective and safer when given in first line of MM therapy compared to the relapsed/refractory setting since (1) the endogenous T-cell population used for manufacturing will be less compromised by high myeloma burden and prior lines of therapy and (2) lower disease burden would be expected to reduce risk of cytokine release syndrome (CRS).

Potential advantages of the 1902 approach are that patients will be at the lowest possible disease burden (after transplant and maintenance therapy) and will have in large part reconstituted immunologically[6] at the time of T-cell collection and CAR T-cell infusion. The 1902 protocol defines high risk based on suboptimal response with upfront therapy, or less than a very good partial response (<VGPR), which identifies a high-risk population that does not completely overlap with the high-risk population identified based on pre-treatment risk stratification schemes such as R-ISS stage. This population has a clear unmet need for which this study tests a promising intervention. The approach will be to evaluate the safety of adding a CAR T-cell in the upfront setting followed by lenalidomide maintenance in a run in.

2. Are there any expected hurdles for CAR-T manufacturing?

Thus far, BMS reported no manufacturing failures for bb2121. Of note, these have all been manufactured in multiply relapsed patients. Regarding logistics of cell manufacture, BMS has committed to manufacturing slots for this trial. The study will utilize the same manufacturing

infrastructure for the commercial product, which will assist with manufacturing success. Still, we anticipate that some manufacturing failures might occur, and allow for additional leukapheresis and a sufficiently long interval to remediate these events. The FDA has requested to be notified upon any manufacturing failures. Slot allocation procedures will be among the standard operations during the enrollment phase of this clinical trial. BMS and the protocol team will have a forecast of allocated slots in the coming months. The initial run in will require a slow staggered accrual, which will simplify the slot allocation. Once the trial is enrolling actively, slot allocation will match with the accrual goal to avoid delays.

3. Why was CR by 6 months after CAR T-cell infusion selected as the primary endpoint?

Data from the STaMINA trial show that, among patients who are not in CR after six months of maintenance therapy, < 10% upgrade their response in the subsequent six months. Furthermore, data from MSKCC show that patients who fail to achieve CR after six months of maintenance therapy have inferior outcomes. Therefore, the six-month CR conversion rate provides an early and clinically relevant efficacy readout. We chose CR as the primary endpoint based on the prior analyses of STaMINA and MSKCC data that relied on the CR benchmark. We will be tracking all response categories, including sCR, and MRD status as secondary endpoints. The target improvement from 10% to 30% is felt to be a clinically meaningful improvement over the reported 10%.

4. There are a number of immune correlative studies included in this protocol. What are the steps taken to minimize the collection of blood and marrow at a single time point?

This clinical trial offers a unique opportunity to elucidate the delicate interaction between CAR-T-Cells and the patients' own immune system/immune microenvironment. We will also be able to study the effects of these factors on immune reconstitution in the setting of CAR-T therapy and lenalidomide maintenance. The immune correlative endpoints are an integral component of the trial and are not considered ancillary studies. A thorough assessment of immune reconstitution, MRD, BCMA expression, and CAR T-cell expansion and persistence will provide critical insights into the underlying mechanisms of tumor immunology. Additional sample collections have been built into the protocol to accommodate planned future research that will be pursued, provided funding can be secured. Proposed future research includes molecular evaluation of MRD, Serum Cytokine and soluble BCMA levels, and detailed Cell-functional and molecular evaluation of T Cells. Consequently, the comprehensive scope of the proposed studies necessitates more frequent sample collections.

To limit the amount of blood or marrow obtained at any given time point, we have minimized the amount of sample required for each assay and have also staggered sample collections. We agree however that the number of samples collected, especially after the bb2121 infusion, are higher than usual trials. These samples are looking at parameters related to expansion and persistence of the CAR T cell product, which is important when assessing how this product performs in the upfront setting.

5. Patients receiving cyclophosphamide + fludarabine followed by bb2121 have exhibited prolonged cytopenias. How will you manage this risk, particularly in the post-transplant setting where hematopoietic reserve may be compromised?

We recognize prolonged cytopenias as an important risk of participation in this study. This protocol has stringent inclusion criteria for baseline hematologic parameters and additional safeguards including (1) exclusion of patients who require anticoagulation, which would increase the risk of bleeding in the event

of prolonged thrombocytopenia, and (2) requirement for adequate stem cell reserve for rescue stem cell infusion. In addition, we specify management guidelines for prolonged cytopenias and require discussion with protocol team in severe cases. There is also a safety run-in with inter-patient staggers to evaluate for prolonged cytopenias that might prevent resumption of maintenance lenalidomide, a stopping rule for excess cytopenias leading to delay or interruption of maintenance lenalidomide, and a stopping rule (and requirement for FDA notification) for any instance in which rescue stem cell infusion is required for severe cytopenias. It is possible, however, that risk of prolonged cytopenias may be lower in the post-transplant population compared to the relapsed/refractory population, which had received median of 7 prior lines of therapy, where bb2121 was initially evaluated.

6. Can you justify the stopping rules applied to the clinical trial?

The stopping rules were recommended by the FDA to focus on CAR T-cell specific toxicities, cytokine release syndrome (CRS), Immune effector Cell Neurotoxicity Syndrome (ICANS), cytopenia and non-relapse mortality. At least two cases of grade 4 CRS or one event of grade 4 ICANS will trigger a DSMB review. For cytopenias or bone marrow dysfunction or failure, there are two rules: 1) the occurrence of any bone marrow failure requiring hematopoietic stem cell rescue will trigger a DSMB review; and 2) if 15% of patients are unable to start lenalidomide maintenance at least 60 days after CAR T cell infusion or once started maintenance unable to sustain therapy due to cytopenias will trigger a DSMB review. The expected NRM at this stage of MM therapy, i.e. many months after an autologous transplant, to be less than 1%. Based on the size of this trial having at most 2 early deaths is sufficient to trigger a review.

7. Why include maintenance with lenalidomide after CAR T-cells?

In the 1902 protocol, we are evaluating CAR T-cell therapy added into standard first-line myeloma therapy, which includes post-transplant lenalidomide maintenance. Post-transplant maintenance is an FDA-approved indication for lenalidomide based on overall survival benefit[1] regardless of depth-of-response, even as it is recognized that those who remain in < VGPR on maintenance have inferior outcomes. In addition, preclinical data suggest a potential benefit of lenalidomide on CAR T-cell function. For the 1902 study, we are continuing this standard maintenance therapy, which would have already been started for patients prior to enrollment and, absent enrollment on this study, would have been continued until progression. The addition of lenalidomide maintenance may have an impact on the expansion of CAR T cell and broadened its therapeutic effect.

8. Why was this dose and schedule chosen for lenalidomide maintenance therapy?

Our guiding principle was to have patients start maintenance therapy as soon as possible since this is the standard of care after autologous transplant. We also considered, however, the potential for cytopenias (particularly thrombocytopenia) at this relatively early post-transplant timepoint following lymphodepleting chemotherapy and possible CRS. The dosing schedule was modified from the STaMINA trial, which used a continuous 28-day cycle to a intermittent 21 day cycle with 7 days of rest. Both regimens are used as standard of care; the preference to an intermittent regimen is to minimize cytopenias. The protocol sets more stringent CBC cutoffs (ANC 1000, platelets 75) for resumption of maintenance early (day 30-90) after CAR T cells; for patients who meet these more stringent cutoffs, patients will start lenalidomide at 10 mg, the standard maintenance lenalidomide dose. For patients who have prolonged cytopenias and do not meet these requirements within 90 days, we relax the CBC requirements after day 90 (ANC 1000, platelets 50) but use a lower dose of 5 mg. It also might help

adherence to the maintenance regimen, based on clinical experiences from members of the protocol team.

9. Why did you choose this patient population?

The objective of 1902 is to evaluate CAR T cell therapy as part of first-line multiple myeloma therapy in patients who have a poor prognosis. For 1902, poor prognosis is defined by inadequate response to first-line therapy. The PRIMeR study, which was an ancillary study to the BMT CTN 0702 analyzed minimal residual disease at different timepoints in the first year after the transplant. Additionally, this study evaluated the impact of serologic response on outcomes. Among patients who are in a partial response or stable disease still at one year after the transplant, there is a substantial risk for treatment failure in the second year after the transplant. The premise of this trial is to upgrade the response and modify the trajectory towards treatment failure.

10. What is the reasoning for staggered enrollment/safety run-in?

Although this clinical trial is directed to patients with high-risk multiple myeloma, the combination of an autologous HCT, CAR T cells and lenalidomide maintenance is novel and have the potential to cause myelotoxicity. Patients eligible for 1902 have not failed therapy, despite being at high risk for failure, and intensive intervention at this stage needs to be safe. The FDA was mostly concerned in assessing safety of this novel approach. Accordingly, the safety run-in with staggered enrollment allows for assessment of excess early toxicity or prolonged cytopenias that limit resumption of maintenance lenalidomide.

11. Can study participants be co-enrolled on another clinical trial?

Decisions regarding whether a BMT CTN 1902 participant can be co-enrolled on another clinical trial will be made by the Protocol Team on a case-by-case basis. Sites will need to email the Emmes Protocol Coordinator (PC) at bmtctn1902@emmes.com to submit a co-enrollment request. Once reviewed by the Protocol Team, the Emmes PC will inform the site of the Protocol Team's decision.

References

[1] McCarthy, P.L., et al., *Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis.* J Clin Oncol, 2017. 35(29): p. 3279-3289.

[2]Durie, B.G, et al, *Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnoses myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial*. The Lancet, 2017. 389(10068):519-527

[3] Raje, N., et al., *Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma.* N Engl J Med, 2019. 380(18): p. 1726-1737

[4] Cohen AD, et al. *B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma.* J Clin Invest. 2019 Mar 21;130:2210-2221. doi: 10.1172/JCI126397.

[5] Brudno JN, et al. *T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma*. J Clin Oncol. 2018 Aug 1;36(22):2267-2280. doi: 10.1200/JCO.2018.77.8084. Epub 2018 May 29.

[6] Chung DJ, et al, *T-cell Exhaustion in Multiple Myeloma Relapse after Autotransplant: Optimal Timing of Immunotherapy*. Cancer Immunol Res. 2016 Jan;4(1):61-71