BMT CTN 2501 FRONTIER: CAR-T for MCL

Phase II Multicenter Trial of MB-CART2019.1 (Zamtocabtagene Autoleucel) Therapy as Frontline Consolidation for High-Risk Mantle Cell Lymphoma

FREQUENTLY ASKED QUESTIONS (FAQs)
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1. Why run a high-risk MCL Phase 2 treatment trial?

Mantle Cell Lymphoma (MCL) is a rare and heterogenous type of B-cell Non-Hodgkin Lymphoma (NHL). While advances in frontline therapy for MCL have improved outcomes for most patients, a subset continues to have particularly poor outcomes. These high-risk patients represent about 10-15% of newly diagnosed MCL, and have a clinical course characterized by early relapse despite intensive therapy, and poor outcomes to subsequent treatments including novel targeted agents and cellular therapy. Identifying strategies to improve outcomes of high-risk MCL patients is a major unmet clinical need. The BMT CTN 2501/FRONTIER-MCL trial is a multicenter single-arm phase II trial, examining the early use of MB-CART2019.1 (Zamtocabtagene Autoleucel, or zamto-cel), a dual-targeting chimeric-antigen receptor T-cell (CAR-T) product, as consolidation to reduce progression and improve survival of patients with newly diagnosed high-risk MCL. In this study, patients with high-risk MCL will receive a single infusion of zamto-cel after 2 cycles of induction therapy. Given the absence of approved CAR-T therapy for frontline MCL, this study is appropriately designed as a single-arm non-randomized study. If successful, the FRONTIER-MCL trial has the potential to inform the design of future trials and change clinical practice.

2. Why was MB-CART2019.1 (Zamtocabtagene Autoleucel) chosen as the experimental agent for BMT CTN 2501?

There are no CAR-T products currently approved for the frontline treatment of MCL. Two autologous CAR-T products, brexucabtagene autoleucel (brexu-cel) and lisocabtagene maraleucel (liso-cel), are approved for relapsed/refractory MCL. Both products target CD19, a protein frequently expressed on lymphoma cells. While these represent a major therapeutic advance in MCL, outcomes with both brexu-cel and liso-cel remain poor in high-risk patients who experience inferior efficacy and durability of response. The loss of CD19 expression by MCL cells has emerged as a key mechanism of resistance. MB-CART2019.1 (zamtocabtagene autoleucel or zamto-cel) is a unique CAR-T product that binds to two antigens - CD19 *and* CD20. This design allows the product to overcome the issue of antigen loss and broaden therapeutic reach. Importantly, MCL cells are known to highly express CD20, making this an attractive target for anti-MCL therapies. Preliminary data on the safety and efficacy of zamto-cel in patients with relapsed/refractory MCL comes from a multi-arm phase I/II trial (NCT0418652). In this trial, n=17 patients with relapsed/refractory MCL, including 50% with high-risk disease, were treated with zamto-cel. The response rate was 100%, with 90% of patients still in response at 1-year. There were no cases of grade 3 cytokine-release syndrome, and only 3 patients experienced immune-cell effector associated neurotoxicity syndrome within 28 days of infusion. Zamto-cel was infused fresh (non-cryopreserved) in 14/17 patients on this study. Several large multi-center clinical trials have since established the feasibility of manufacturing and treating patients with fresh non-

cryopreserved zamto-cel product. Taken together, the results from these studies provide early evidence that dual targeting of CD19 and CD20 with zamto-cel can result in deep and durable remissions with a favorable toxicity profile in this setting. For this reason, zamto-cel was chosen as the experimental agent for BMT CTN 2501 to be used as consolidation in high-risk MCL patients.

3. What is the primary endpoint and why?

The primary endpoint of this study is progression-free survival (PFS) at 1 year following MB2019.1 CAR-T infusion. Events for PFS represent clinical progression and death from any cause. The contemporary 1-year PFS for patients with high-risk MCL is estimated to be around 55%. This study is powered to detect an improvement of 20% from this historical benchmark. PFS was chosen as the primary endpoint because it provides a meaningful surrogate for overall survival - capturing both progression and treatment-related mortality and enabling the assessment of safety and efficacy in this high-risk population without the need for prolonged follow up.

4. Are pediatric cases eligible?

No, this protocol requires patients be at least 18 years of age to consent and participate.

5. Is any interim (efficacy or futility) analysis planned?

Interim analysis will be performed for safety only, not for efficacy or futility.

6. Is there a need for a multi-center network to meet the objectives?

Yes. MCL is a rare disease, and high-risk MCL accounts for 10-15% of newly diagnosed cases. No single center treats enough patients to complete accrual in a meaningful time frame.

7. Is the accrual goal feasible?

Yes. Please see separate accrual plan document.

8. Are there any specific study training plans necessary to accomplish the research?

No.

9. Accrual Estimates

Please see separate accrual plan document.

10. Why is infusion of the CAR-T product allowed prior to receipt of the final sterility testing?

This product is delivered as a FRESH product and as a result, final sterility cultures will not be resulted at the time of the infusion. In-process testing is performed to ensure the product is safe, at the right dose, and free of infection. If a sterility culture returns positive post-infusion, centers will be notified so appropriate interventions can take place.

11. Why are only two cycles of induction allowed prior to CAR-T therapy?

The main aim of this study is to examine the safety and efficacy of early use of zamto-cel as consolidation therapy in high-risk MCL patients. These patients are at high risk for early relapse. It is therefore imperative to capture these patients early in the course of their treatment. In addition, there is concern that the prolonged use of bendamustine can reduce the ability to

effectively manufacture CAR-T cells. Given that confirmation of high-risk MCL features may require several weeks for diagnostic and molecular testing, two cycles of induction therapy was selected to balance the need for prompt disease control with the practical considerations of patient identification, eligibility confirmation, and timely enrollment, while minimizing potential adverse effects on CAR-T cell production.

12. Will bendamustine treatment be allowed prior to CAR-T infusion?

Yes, because bendamustine is commonly incorporated into standard-of-care induction regimens for MCL, prior exposure will be allowed. Based on available data from existing trials, including in the relapsed/refractory setting, limited exposure to bendamustine is not expected to meaningfully compromise CAR-T manufacturing.

13. Will the study allow patients with CNS disease?

Yes, the study will allow patients with leptomeningeal CNS disease, but eligibility requires that the disease is not currently active.