BMT CTN 2303 SR aGVHD

A Single-Arm, Multicenter, Pivotal Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells (MSCs), for the Treatment of Grade II-IV Acute GVHD That Failed to Respond to Both First-line and Second-line Therapy

FREQUENTLY ASKED QUESTIONS (FAQs)
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1. Why run a third-line treatment study instead of second-line?

Patients with acute Graft-versus-Host Disease (aGVHD) resistant to both steroids and second-line treatment, usually ruxolitinib, have a very poor prognosis. A Phase 2 study evaluating ruxolitinib for treatment of steroid-refractory aGVHD (REACH1) showed an overall response rate (ORR) at day 28 (D28) of approximately 55%, leading to the FDA approval of ruxolitinib in May 2019. However, in the subsequent phase III randomized clinical trial (REACH2), despite 62% ORR by D28, the durable response rate at D56 was only about 40%. This means that more than half of patients receiving second-line ruxolitinib will need further therapy; however, there is no currently available agent with proven efficacy in this setting. Given the dismal overall outcomes in patients with steroid refractory aGVHD (SR-aGVHD) failing second-line treatment, this represents an important unmet medical need and innovative approaches are urgently needed. Such patients should be treated on multicenter clinical trials using agents with apparent or demonstrated efficacy for treatment of refractory aGVHD. BMT CTN is an ideal platform for such a study.

2. What are the lines of therapy for aGVHD and how is SR-aGVHD defined in this trial?

Current FDA definition of steroid resistance, for the purpose of testing second-line treatments, requires aGVHD to progress or fail to improve after treatment with methylprednisolone equivalent (MPE) ≥2 mg/kg/day. However, this criterion does not reflect actual current practice and would unnecessarily restrict patients from participation in a third-line treatment trial, at a time when there is no opportunity to alter how the physician initially treated the patient.

Patients eligible for this study must have failed two lines of therapy, including steroids. A line of treatment for aGVHD is defined as an introduction of a systemic treatment (or several drugs simultaneously), not previously used, for treatment of aGVHD. If different treatments (including steroids) are initiated ≤3 days of each other, they are considered one line of therapy. Patients can meet the criteria for steroid resistance if their maximum steroid dose prior to initiation of study treatment was at least 1 mg/kg/d of MPE, which acknowledges real world practice where 70% of patients receive doses between 1 and 2 mg/kg/d for initial treatment of a GVHD (MAGIC unpublished data).[1,2,3]

The minimum time between second-line treatment and enrollment is 3 days if aGVHD has progressed in at least one organ regardless of improvement in other organs; 7 days for aGVHD showing no improvement in any involved organ(s) other than skin; or 7 days if aGVHD recurred after an initial response to second line therapy. Patients with aGVHD involving liver and/or gastrointestinal system (GI) have more severe disease with greater impact on survival. Improvement in skin stage does not negate the poor prognosis of persistent liver or GI aGVHD.[4,5,6]

3. Why should we test MSCs given a failed earlier trial?

The biological activity of MSCs provides a mechanistic rationale for their investigational use in aGVHD. A first generation remestemcel-L product, called Prochymal, failed to meet its Day 28 overall survival primary endpoint in a trial in adults (Study 280). Substantial manufacturing changes were introduced by Mesoblast to improve the MSC product. It resulted in a significantly more potent 2nd generation remestemcel-L product, Ryoncil, based on potency assays which measure the effects of the product on T-cell activation and function relevant to the aGVHD process. The increased potency of Ryoncil relative to Prochymal is demonstrated using well-characterized potency assays. The clinical superiority of the 2nd generation Ryoncil product is evident when long-term outcomes (i.e., day 100 overall survival) are compared between the 93 subjects who received only Ryoncil drug product lots and 115 subjects who received only Prochymal drug product lots (74% vs 57%, p=0.0076). The proposed clinical trial will use only the high potency Ryoncil product, released based on the exact same potency assays as were used to release product in the successful Phase 3 trial in children.

4. Why was Day 28 response selected as the primary endpoint?

D28 ORR is recommended by the FDA as the primary endpoint for aGVHD treatment trials and will be used in this study. The preliminary data with remestemcel-L in 25 patients 12 years or older (median age 17 years) showed a D28 ORR of 68%. This study is powered assuming a more conservative D28 ORR of 56%. The observed ORR must be at least 36% to be within the 95% confidence interval of a true 56% response rate.

Mesoblast data shows that patients often deepen their response between D28 and D56, with increasing numbers of complete responses (CR) by D56. Therefore, in the absence of progression, patients will continue to receive the study drug through D56. CR at D56 will be one of the secondary endpoints. Additionally, we have designed another secondary endpoint, D100 Failure Free Survival, a composite endpoint incorporating two meaningful criteria: response by D56 and survival to D100 without clinically significant progression of aGVHD, as a measure of clinically meaningful response.

5. What is the justification for a single arm treatment design?

- FDA acknowledges the appropriateness of single arm trial designs for third-line treatment of aGVHD in the guidance published in September 2023.
- The available clinical data demonstrating acceptable outcomes following treatment with remestemcel-L together with the universally poor outcomes with other treatments indicate a lack of equipoise.
- A cross-over trial design is not appropriate given the short median survival for patients who develop highly treatment-resistant aGVHD.
- There is no established third-line treatment and the control arm, represented as “best available therapy”, would consist of highly heterogeneous treatments with very different side-effect profiles.
- The population of patients who require third-line treatment is relatively small and the sample sizes required for a randomized study are not feasible.

6. Are pediatric patients < 12 eligible?

No, patients should be at least 12 years of age. A prior study[7] demonstrated efficacy of remestemcel-L in patients <12 and FDA-approval of remestemcel-L for this group is expected in the first quarter of 2025, with the product being available commercially. In this study, we are focusing on determining whether patients age ≥12 also benefit from this product.

7. Is this trial feasible?

We acknowledge that SR-aGVHD is a rare disease (~5% of allotransplant recipients will need third-line aGVHD therapy) Consequently, it requires the resources of a large cooperative group such as the BMT CTN to enroll a sufficient number of patients in a reasonable timespan. Although the number of patients is small, the population is similar in size to other rare diseases for which the BMT CTN has conducted successful trials. The accrual projections are based on CIBMTR data on this patient population from the BMT CTN centers.

8. Is prior donor leukocyte infusion (DLI) allowed?

DLI for treatment of malignant disease relapse within 60 days in an Exclusion Criteria because of the uncertainty of adequacy of malignant disease control in these patients. Overt relapse would complicate the assessment of response. Additionally, these patients often receive additional chemotherapy, putting them further at risk for infections and other adverse events that would compromise evaluation of safety.

Patients who received DLI for indications other than frank relapse, including for minimal residual disease (MRD) or mixed chimerism, are eligible. Patients who received DLI for MRD positive status should have a repeat MRD testing prior to enrollment, showing MRD negative status.

9. Are patients with overlap GVHD syndrome eligible?

Overlap GVHD syndrome (e.g. simultaneous presence of aGVHD and features of chronic GVHD requiring systemic treatment) is an Exclusion Criteria, considering that previous studies have shown worse survival in those patients.[8,9] Including patients receiving systemic treatment for active chronic GVHD would also confound the assessment of response. Patients with chronic GVHD that is no longer active and/or not requiring systemic therapy are eligible.

10. Why are patients that undergo a second transplant excluded?

Patients who have undergone a second transplant have higher rates of complications which can confound assessments of response and safety.

11. Is it permissible to continue other medications for aGVHD used for prophylaxis or treatment?

It is permissible to continue agent(s) used for aGVHD prophylaxis including: CNI (e.g., tacrolimus or cyclosporine), mTOR inhibitors (e.g., sirolimus), and/or MMF, and they are not considered a line of treatment for aGVHD. If an agent used for prophylaxis of aGVHD (e.g., CNI, mTOR inhibitor, or MMF) was previously discontinued, and then restarted at the time of aGVHD, re-institution of the prophylactic agent is permissible and is not considered a line of therapy.

While the protocol allows for continuation of second-line treatment(s) that the patient is receiving at the time of enrollment (e.g. ruxolitinib), it also strongly recommends discontinuation of drugs that failed as prior treatments for aGVHD, in accordance with the September 2023 FDA draft guidance for GVHD treatment trials. If a second-line treatment is discontinued at the time of enrolment, but re-started later throughout the trial, it is considered a treatment failure.

12. Can steroids be tapered on the study?

Steroids may be tapered at investigator discretion after at least 3 days on the study. A steroid taper rate between 10% and 25% per week is recommended. If aGVHD flares during the steroid taper, the dose may be re-escalated at the investigator's discretion and this will not be considered a treatment failure, as long as the dose does not exceed the initial starting dose by 20%.

13. What are the proposed plans for data acquisition, transfer, management, and analysis?

A web-based data entry platform will be used to collect study data. Data are transmitted via an encrypted link between the web server and browser using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Electronic Case Report Form Guide will be developed for reference.

Missing forms reports are updated daily. Queries will be developed to check for missing and inconsistent data. Queries will be distributed to the centers at least monthly.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the protocol and statistical analysis plan (SAP).

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

Site staff will need to participate in a Site Initiation Call, the PI and staff will need to have documented training on the protocol, study coordinators will need to be trained on data entry for the study, and manuals for pharmacy and laboratory specimen collection will be developed for site staff to be trained on as well.

15. Is interim analysis planned?

There will be no interim analyses for efficacy nor futility, given the small sample size and the well-established safety profile of MSCs. However, mortality at Day 100 will be monitored throughout the study. A mortality rate of 70% during the first 100 days would be considered unacceptable as compared to the historical rate of 50% and would trigger a DSMB review (not the formal stopping rule).

16. Accrual Estimates

Please see separate accrual plan document.

References

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