BMT CTN 2303 REVIVE

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial of remestemcel-L-rknd added to ruxolitinib for Grade III-IV Steroid-Refractory Acute Graft-Versus-Host Disease

FREQUENTLY ASKED QUESTIONS (FAQs)
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1. Why should we test mesenchymal stromal cells (MSCs) given a failed earlier trial?

The biological activity of MSCs provides a mechanistic rationale for their investigation in treating acute GVHD (aGVHD). A first generation MSCs product remestemcel-L, 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. These resulted in Ryoncil, a significantly more potent 2nd generation remestemcel-L product based on well-characterized potency assays which measure effects of the product on T-cell activation and function relevant to the aGVHD process. The clinical superiority of the 2nd generation Ryoncil product was demonstrated in a comparison of Day 100 overall survival of 93 subjects who received Ryoncil and 115 subjects who received Prochymal (74% vs 57%, p=0.0076); Mesoblast retrospective analysis. Clinical data on the efficacy of Ryoncil in children led to FDA approval for its use in pediatric patients with steroid refractory aGVHD (SR-aGVHD) in 2024. The Day 28 (D28) response rate in the trial leading to approval was 70.4%.

The variability in potency from lot-to-lot is 5% which is entirely due to the variability in the FDA validated and qualified potency assay since a similar level of variability is seen when the same lot is measured repeatedly. Any two lots of Ryoncil that meet the sponsor's minimum potency release criteria will have the same clinical efficacy.

2. Why are we presenting a new protocol design?

Our initial protocol was designed as a single arm study of remestemcel-L as 3rd line treatment for SR-aGVHD. The protocol was discussed with FDA at a Type C meeting in July 2025. The FDA did not agree with the single-arm trial design and recommended a randomized controlled trial (in 2nd or 3rd line). The FDA also stipulated that D28 overall response rate (ORR) should be the Primary Endpoint and suggested that testing ruxolitinib + remestemcel-L/placebo would be an acceptable trial design.

Treatment failure remains a major problem for patients with SR-aGVHD despite numerous prior studies and the recent approval of ruxolitinib. The need for better treatment is especially important for patients at the highest risk for treatment failure, specifically those with Grade III/IV SR-aGVHD. The BMT CTN protocol 2303 is now designed as a randomized, double-blind, placebo-controlled, multicenter Phase III trial to compare the efficacy and safety of remestemcel-L combined with ruxolitinib vs. ruxolitinib combined with placebo as 2nd line therapy in adults with Grade III-IV SR-aGVHD. The study will test the hypothesis that the combination of remestemcel-L plus ruxolitinib will be a more effective 2nd line treatment for Grade III-IV SR-aGVHD, resulting in an improved ORR.

3. Is there a negative effect of combining remestemcel-L and ruxolitinib ?

The clinical data available, although limited, for the combination of MSCs and ruxolitinib suggest no negative effects. There is a theoretical consideration that ruxolitinib may dampen inflammatory signals that are possibly necessary to license and activate MSCs, however this concern is offset by the highly inflammatory setting of Grade III/IV SR-aGVHD. An analysis of patients 12 years and older who received remestemcel-L for 3rd line treatment of SR-aGVHD on a Mesoblast EIND showed similar Day 100 survival (~80%) in patients who received ruxolitinib as 2nd line treatment (n=11) and those who did not have prior ruxolitinib exposure (n=14). Both agents are FDA approved, with different mechanisms of action and non-overlapping toxicities. It is not anticipated that the addition of remestemcel-L to ruxolitinib will increase hematologic toxicity significantly above that due to ruxolitinib, because of the very low incidence of grade 3 and 4 hematological toxicities associated with the use of remestemcel-L.

4. Is this trial feasible?

We acknowledge that SR-aGVHD is a rare disease (~10-15% of allotransplant recipients will need 2nd line aGVHD therapy; MAGIC database). However, treatment failure is a major problem for these patients despite the use of ruxolitinib and few other treatment options available. Therefore, this trial addresses an unmet need. However, 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. Accrual projections are based on CIBMTR data on the incidence of aGVHD in recent years and MAGIC data on response to therapy. We anticipate that approximately 35 centers will open this trial and that 180 patients (5-6 patients/center) will be enrolled over 30 months.

5. How is SR-aGVHD defined in this trial?

The current FDA definition of steroid resistance, for the purpose of testing 2nd line treatments, requires aGVHD to progress or fail to improve after treatment with the 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 2nd line treatment trial.

In this trial, 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 aGVHD (MAGIC unpublished data).[1,2,3]

6. Why was D28 response selected as the primary endpoint?

D28 ORR (complete response [CR] + partial response [PR]) is recommended by the FDA as the primary endpoint for aGVHD treatment trials and will be used in this study.

Remestemcel-L was approved by FDA for the treatment of SR-aGVHD in pediatric patients based on results of MSBGVHD001, a Phase III single arm, multicenter study that enrolled 54 pediatric patients, with ORR at D28 of 70.4%. Day 14 ORR was 68.5%.

We don't know how long responses will take to develop in this study, although responses to ruxolitinib typically begin within 2 weeks of starting the drug. However, since remestemcel-L used as a single agent in 2nd line therapy of pediatric SR-aGVHD induces similar ORR at Day 14 and D28, it is reasonable to expect that ORR will be mature by D28 in most patients randomized to the combination of remestemcel-L and ruxolitinib, even if a small number of doses of either, or both agents, are missed before D28.

7. How is the Primary Endpoint defined?

Primary Endpoint is defined as ORR (CR+PR) without progression or new intervening systemic therapy at D28 post randomization.

8. What is the rationale for Day 56 assessment and Continued Therapy?

Mesoblast data shows that patients often deepen their response between D28 and Day 56 (D56), with increasing numbers of complete CRs by D56. Therefore, patients who achieve PR or mixed response (MR) at D28 assessment will continue to receive the study drug through D56. Response at D56 will be a secondary endpoint. Patients with CR, progression or no response (NR) at the D28 assessment, will not continue the study drug therapy.

Similar to the prior pediatric trial, patients achieving MR at D28 will continue the study drug through D56. In addition, patients achieving MR will continue ruxolitinib through D56. MR is defined as a failure of primary endpoint, but response and survival will be captured as secondary endpoints.

9. How is treatment failure defined?

Treatment failure is defined as responses categorized as NR, MR, progression, or addition of new intervening systemic immunosuppressive agent for treatment of aGVHD, or death.

We consider lost-to-follow-up as a failure for the trial's endpoint, including the primary endpoint. Nevertheless, we anticipate a low rate of loss-to-follow-up in this very sick population.

10. 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 calcineurin inhibitors (e.g., tacrolimus or cyclosporine), mTOR inhibitors (e.g., sirolimus), and/or mycophenolate mofetil (MMF), including if they were restarted at the time of aGVHD diagnosis as a part of primary treatment. It is not permissible to restart these agents after enrollment. Dose adjustments of prophylactic agents to maintain their level therapeutic or changes in the route of administration are allowed.

Prior use of ruxolitinib for prophylaxis of GVHD is allowed unless aGVHD developed while on ruxolitinib or within 3 days of its discontinuation for GVHD prophylaxis. Participants that have started ruxolitinib for treatment of SR-aGVHD are allowed to receive 2 doses of ruxolitinib during the 24 hours prior to randomization.

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

12. 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.

13. Why are patients that undergo a 2nd transplant within six months from the 1st transplant excluded?

Patients who have undergone a 2nd transplant soon after the 1st transplant have higher rates of complications which can confound assessments of response and safety.

14. Can steroids be tapered on the study?

Steroids may be tapered at investigator discretion after at least two doses of the study drug. 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 120% of the initial starting dose.

15. How long does ruxolitinib continue on the study?

Patients who achieve CR, PR or MR at D28 will continue ruxolitinib through D56, after which it may be tapered at investigator's discretion. In patients who achieve NR or who progress by D28, ruxolitinib can be discontinued per investigator's discretion.

16. Who will be blinded on this double-blind study?

Everyone will be blinded except the personnel preparing the study drug product for the infusion. The placebo will be manufactured using Mesoblast's current manufacturing facility and will be supplied in cryogenic vials containing the excipients Plasma-Lyte A, 10% DMSO, and human serum albumin as per manufacturing of remestemcel-L-rknd but without the cells. Placebo will be shipped to each participating transplant center in the cryopreserved state and should be stored and kept at ≤ 135°C until thawed for infusion. Any residual thawed product should be discarded using institutional standard biohazard precautions for cellular products.

17. How long does it take for cells to arrive once a patient is enrolled on trial?

Each site will have at least one dose of study drug (e.g., remestemcel-L and placebo) on site at any time. Cells will be shipped to sites during the site activation process in order to prevent delays in starting treatment once a patient is identified. Once shipped, cells arrive to the site in approximately 24-48 hours.

18. 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).

19. 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.

20. Is interim analysis planned?

One interim analysis for efficacy and futility will be conducted when approximately 108 participants are enrolled, 102 participants have been followed for the primary ORR endpoint (57% information fraction) assuming enrollment of approximately 6 participants per month, and the expected information for the key secondary OS endpoint is approximately 50% of the targeted 72 events.

21. Accrual Estimates

Please see separate accrual plan document.

References

1. Mielcarek, M. et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica* **100**, 842–848 (2015).
2. Mohty, M. et al. Refractory acute graft-versus-host disease: a new working definition beyond corticosteroid refractoriness. *Blood* 136, 1903–1906 (2020).
3. Malard F, Huang XJ, Sim JPY. Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia. 34(5):1229-1240 (2020).
4. MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. Biol Blood Marrow Transplant, 21(4): 761-767 (2015),
5. Castilla-Llorente C, Martin PJ, McDonald GB, et al. Prognostic factors and outcomes of severe gastrointestinal GVHD after allogeneic hematopoietic cell transplantation. *Bone Marrow Transpl,*49:966-71 (2014).
6. Vo P, Gooley TA, Carpenter PA, et al. Prediction of outcomes after second-line treatment for acute graft-versus-host disease. Blood Adv Jun 14;6(11):3220-3229 (2022).
7. Kurtzberg J, Abdel-Azim H, et al. A Phase 3, Single-Arm, Prospective Study of Remestemcel-L, Ex Vivo Culture-Expanded Adult Human Mesenchymal Stromal Cells for the Treatment of Pediatric Patients Who Failed to Respond to Steroid Treatment for Acute Graft-versus-Host Disease. BBMT 2020;26(5):845-54.
8. Moon JH, Sohn SK, Lambie A, et al. Validation of National Institutes of Health global scoring system for chronic GVHD according to overall and GVHD-specific survival. Biol Blood Marrow Transplant: J Am Soc Blood Marrow Transplant. 20:556–63 (2014).
9. Schoemans HM, Lee SJ, Ferrara JL et al. EBMT−NIH−CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. BMT; 53: 1401–1415 (2018).