BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 2002/XEN-TG-005

A Phase 3, Randomized, Open-Label, Multicenter Study, to Compare T-Guard to Ruxolitinib for the Treatment of Patients with Grade III or IV Steroid-Refractory Acute Graft-Versus-Host Disease (SR-aGVHD)

FREQUENTLY ASKED QUESTIONS (FAQs)
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1. Why run a steroid refractory acute GVHD Phase 3 treatment trial?

Despite improvements in post-transplant survival over the last decade, steroid-refractory acute graft-versus-host disease (SR-aGVHD) remains the leading cause of non-relapse mortality, with a mortality rate of 70-80% (1). Deaths are driven by both poor response to salvage treatment and serious infectious complications due to profound immunosuppression. SR-aGVHD remains an area of great unmet medical need and the only FDA approved treatment (ruxolitinib) has limited effectiveness for patients with severe Grade III/IV SR-aGVHD. New treatments are needed and should be compared to ruxolitinib to assess their place as a treatment option.

2. How is steroid refractory acute GVHD defined in this trial?

BMT CTN 2002 defines SR-aGVHD as the following:

SR-aGVHD includes aGVHD initially treated at a lower steroid dose, but must meet one of the following criteria:

- disease progression or new organ involvement after 3 days of treatment with methylprednisolone (or equivalent) of greater than or equal to 2 mg/kg/day
- no improvement after 7 days of primary treatment with methylprednisolone (or equivalent) of greater than or equal to 2mg/kg/day
- patients with visceral (GI and/or liver) plus skin aGVHD at methylprednisolone (or equivalent) initiation with improvement in skin GVHD without any improvement in visceral GVHD after 7 days of primary treatment with methylprednisolone (or equivalent) of greater than or equal to 2mg/kg/day

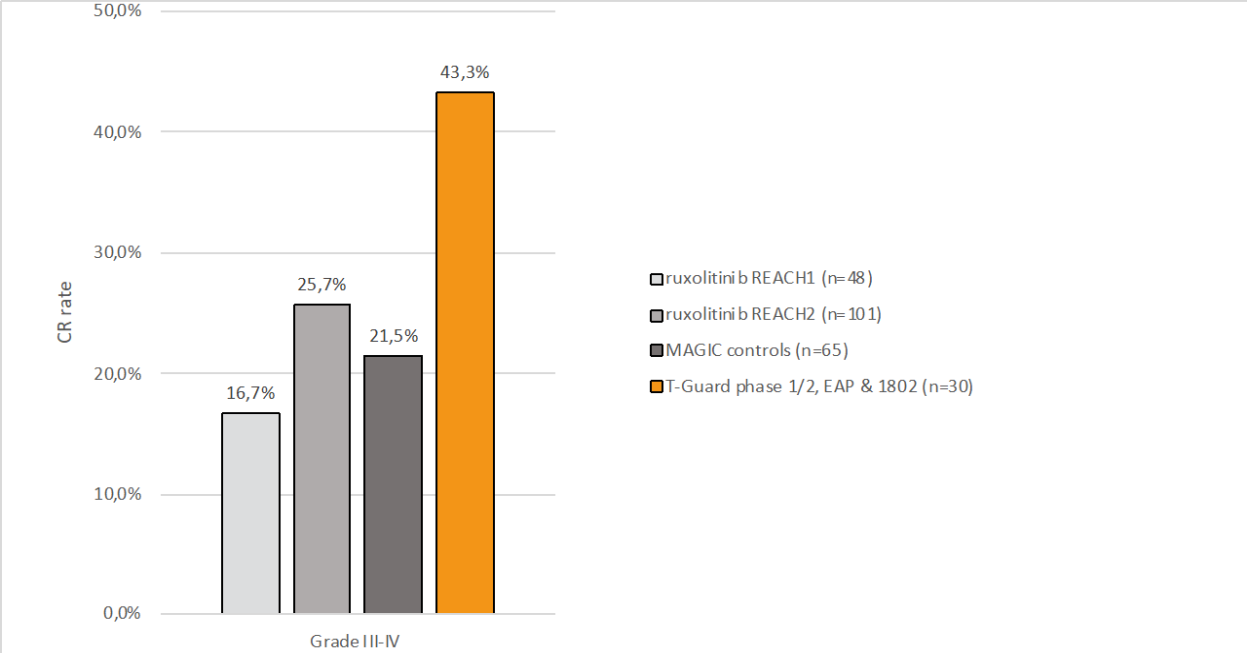
3. Why was T-Guard chosen as the experimental agent for BMT CTN 2002?

T-Guard is an immunotoxin-combination consisting of equal amounts of murine monoclonal antibodies against CD3 and CD7, each individually conjugated to the Ricin Toxin A (RTA) chain: SPV-T3a-RTA and WT1-RTA. T-Guard resulted in a relatively high complete response rate for patients with Grade III/IV SR-aGVHD relative to ruxolitinib or historical controls treated with best available therapy (Figure 1).

Ruxolitinib was chosen as comparator, because it has shown to be efficacious for treatment of SR-aGVHD in the REACH1 and REACH2 trials. A sub analysis of the REACH1 data resulted in FDA approval for the treatment of SR-aGVHD patients in May 2019 (Przepiorka et al. 2020). The REACH2 trial represents the first randomized trial that successfully proved a compound to

be superior to BAT, following a period of 30 years with numerous Phase 2 trials and 2 previous Phase 3 trials, in which no treatment really stood out over other treatments (Zeiser et al. 2020).

Figure 1: Day 28 CR rates Grade III-IV SR-aGVHD Patients



4. What is the rationale for selecting a combination of anti-CD3 and anti-CD7 immunotoxins in T-Guard for treatment of steroid refractory acute GVHD?

Preclinical data suggest that this combination harbors relevant properties for clinical use (e.g., synergistic killing of T-cells, with a preference for recently activated T-cells (which have a higher expression of CD7) and a relative sparing of non-activated T-cells and anti-viral cells, transient depletion of NK cells, and additive immunosuppression provided by the modulation of the CD3/TCR complex). Moreover, due to the short one-week administration period in combination with T-Guard's short half-life (only 7-9 hours), the lymphocytopenia induced by T-Guard is considerably shorter than what is typically observed after other lymphodepleting agents like alemtuzumab and ATG.

5. What is the primary endpoint and why?

Day 28 CR rate is selected as primary endpoint given the consensus that achieving a CR is clearly driving long-term OS in patients with SR-aGVHD [1-4]. Day 28 CR has been accepted by the regulatory authorities as primary endpoint.

6. Are pediatric cases eligible?

No, patients should be at least 18 years of age. After the safety run-in, the DSMB may evaluate whether adolescents could be included through protocol amendment. Further studies in children <12 will be performed as per the Pediatric plan (following more data being available in adults and adolescents next).

7. Are patients with previously treated steroid-refractory acute GVHD eligible?

No. The preliminary data generated for this approach was obtained from patients who had not already been treated for SR-aGVHD. It is not known whether patients who have already failed other treatments for SR-aGVHD will have similar response rates to T-Guard or ruxolitinib.

8. Why are patients with severe hypoalbuminemia (i.e., serum albumin of <1 g/dL) or elevated creatine kinase (i.e., CK level greater than 5 times upper limit of normal) being excluded?

The most common side-effects described for RTA-based immunotoxins are capillary leak syndrome (CLS) and myalgia, the latter being often associated with an increase in serum creatine kinase (CK). Although no severe cases of CLS have been reported for T-Guard treated patients, excluding patients with severe hypoalbuminemia further mitigates the risk of serious complications from CLS. The same holds true for myalgia. Monitoring for the development of myalgia, with subsequent CK testing if present, is important for those patients receiving T-Guard.

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

This trial will include three interim analyses, one for futility and two for efficacy.

Futility:

This trial will include one interim analysis for futility after 23 patients on the T-Guard arm (46 patients total) become evaluable for the primary endpoint.

Efficacy:

After 150 patients reaching Day 28, two sets of analyses will be performed to test whether T-Guard's Day 28 CR rate is superior to:

1. historical Best Available Therapy (BAT) to support T-Guard approval from US regulatory authorities (FDA). An earlier futility analysis will take place after 46 patients reaching Day 28.
2. ruxolitinib treatment to support T-Guard approval from European regulatory authorities (EMA). If superiority is not found in this group of 150 patients, a final analysis will follow once all 246 patients have completed the Day 28 assessment.

10. Why are there two efficacy analyses?

The efficacy analyses are designed to meet the approval requirements for both the FDA and EMA.

11. Why is the study monitoring CMV and EBV reactivations? Will the budget cover such testing?

Viral reactivation/infections are common in patients with SR-aGVHD. While the pre-clinical data suggest that T-Guard preferentially targets activated T cells (partially preserving anti-viral activity), monitoring the frequency and severity of viral reactivations and/or infections is an important safety outcome. The studies with ruxolitinib have also shown CMV reactivation to be a common adverse event. CMV reactivation monitoring by serial PCR is a universally accepted

standard clinical practice for patients with GVHD and is considered part of routine clinical care in this study. The BMT CTN 2002 budget will cover EBV and CMV viral monitoring at the protocol specified time points in as far as they deviate from local routine practice.

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

Yes. Although SR-aGVHD is not a rare post-transplant complication, no single center treats sufficient numbers of SR-aGVHD patients to complete this study within a reasonable timeframe.

13. Is the accrual goal feasible?

Yes, the accrual projections are based on recent surveys of interested centers and realistic projections based on prior experience from the BMT CTN and the European centers.

14. 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 Data Management Handbook 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 statistical analysis plans outlined in the protocol.

15. 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.

16. Will patients treated with DLI be allowed?

Patients that have been proactively or preemptively treated with DLI will be allowed; however, patients who receive DLI for GVHD relapse will be excluded.

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

Patients who have undergone a second transplant have higher rates of complications which can obscure a safety signal in this high-risk population.

18. Why is ruxolitinib being supplied for different lengths of time by the study?

Due to the international nature of this study, there are some countries that will not be able to have their patients continue with treatment on ruxolitinib without a supply from the study. Countries that cannot provide ruxolitinib to their patients off-study will be able to receive ruxolitinib for up to six months from the study. Whereas countries that can provide ruxolitinib off-study will receive ruxolitinib through Day 56 from the study and if their physician decides to continue ruxolitinib the patients can get ruxolitinib from a local pharmacy.

19. Sample size is based on the 17% difference in response. Should a more conservative approach be utilized?

The expected difference is based on the observed outcomes in the REACH2 study and is more conservative compared to the outcomes observed across the entire ruxolitinib trial outcomes.

20. Does T-Guard have bone marrow toxicity?

T-Guard has not been associated with bone marrow toxicity in any of the treated patients. Moreover, non-clinical experiments have not shown a negative impact of anti-CD3 and anti-CD7 immunotoxins on hematopoietic progenitor cells (Preijers et al, Scand. J. Immunol. 27, 533-540, 1988). The hematological toxicity reported for T-Guard is reversible thrombocytopenia.

21. If patient is refractory to T-Guard, can this patient be given ruxolitinib or other medication?

Patients refractory to T-Guard may be administered ruxolitinib or other salvage treatment per the discretion of the treating physician. However, study treatment cross-over will not be permitted.

22. Why is salvage treatment allowed after 7 or 14 days?

The median duration until improvement of at least one Grade after the first T-Guard infusion in patients with Grade III and IV SR-aGVHD, was 7 days with an interquartile range (IRQ) of 3 to 14. Furthermore, in those with a response (CR or PR; 19 out of 30) in 95% (18/19) of the patients this response occurred within 14 days of the first T-Guard infusion and in 37% (7/19) of the patients in the window day 8 to 14.

In the REACH2 study addition of any new systemic immunosuppressive therapy was allowed 7 days after randomization for patients meeting aGVHD criteria for progression, mixed response or no response criteria.

According to Mohty et al 2020, ruxolitinib-refractory aGVHD is defined as disease that shows (i) progression of GVHD compared to baseline after at least 5 to 10 days of treatment with ruxolitinib, based either on objective increase in stage/grade, or new organ involvement; (ii) lack of improvement in GVHD (PR or better) compared to baseline after at least 14 days of treatment with ruxolitinib.

23. Accrual Estimates

Please see separate accrual plan document.

References

1 Groth, C. *et al.* Phase I/II Trial of a Combination of Anti-CD3/CD7 Immunotoxins for Steroid-Refractory Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant* **25**, 712-719, doi:10.1016/j.bbmt.2018.10.020 (2019).

2 van Groningen, L. F. *et al.* Combination Therapy with Inolimomab and Etanercept for Severe Steroid-Refractory Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant* **22**, 179-182, doi:10.1016/j.bbmt.2015.08.039 (2016).

3 Jagasia, M. *et al.* Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. *Blood* **135**, 1739-1749, doi:10.1182/blood.2020004823 (2020).

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