PROTOCOL SYNOPSIS – BMT CTN 1802 PROTOCOL

An Open-Label, Single-Arm, Multicenter Study of T-Guard for Steroid-Refractory Acute Graft-versus-Host Disease

Co-Chairs:

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Study Design:

The study is an open-label, single arm Phase III, multicenter trial, which has been designed to evaluate the efficacy and safety of T-Guard treatment in patients with Steroid-Refractory acute Graft versus Host Disease (SR-aGVHD).

The primary analysis will include all patients that initiate T-Guard treatment.

Primary Objective:

To assess the rate of Day 28 complete response (CR) in SR-aGVHD patients treated with T-Guard therapy.

Secondary Objectives:

Secondary objectives are the following:

1. Evaluate the duration of complete response (DoCR)
2. Estimate the overall survival (OS) at Days 90 and 180
3. Estimate the overall response rate (CR or partial response (PR)) at Days 14, 28, and 56
4. Describe proportions of CR, PR, mixed response (MR), no response (NR), and progression of aGVHD at Days 7, 14, 28, and 56
5. Estimate the cumulative incidence of non-relapse mortality (NRM) at Days 100 and 180
6. Estimate relapse-free survival at Day 180
7. Estimate GVHD-free survival at Days 90 and 180
8. Estimate the cumulative incidence of chronic GVHD (cGVHD) at Day 180
9. Estimate the cumulative incidence of disease relapse/progression at Day 180
10. Describe the incidence of systemic infections
11. Describe the incidence of toxicities
12. Assess the pharmacokinetics of T-Guard
13. Assess the immunogenicity of T-Guard

Exploratory Objectives:

1. Describe corticosteroid-dose (measured in prednisone-equivalent) at baseline, Days 28 and 56 post initiation of T- Guard therapy.
2. Estimate the rate of near-CR (i.e. CR in GI and Liver with only Stage 1 Skin) at Days 28 and 56 post initiation of T-Guard therapy.
3. Describe discontinuation of systemic steroids by Day 180 post initiation of T-Guard therapy.

4. Estimate the incidence of CMV reactivation requiring therapy by Day 180 post initiation of T-Guard Therapy.
5. Estimate the incidence of Epstein-Barr Virus (EBV)-associate lymphoproliferative disorder or EBV reactivation requiring therapy with rituximab by Day 180 post initiation of T-Guard therapy.
6. Describe the incidence of Investigational Medicinal Product (IMP) related SAEs.
7. Evaluate T-cell subsets and Natural Killer (NK) cells at baseline and at Days 0, 2, 4, 6 (just prior to and 4 hours after each T-Guard infusion) and then subsequently at Days 14, 28, 56, 180.
8. Evaluate aGVHD biomarkers at baseline and at Days 7, 14, and 28 post initiation of T-Guard therapy.
9. Describe changes in patient-reported outcomes (PROs) from baseline to Days 28, 56, and 180 post initiation of T-Guard therapy.

Correlatives:

The pharmacokinetics and immunogenicity of T-Guard will be evaluated as referenced in the secondary and exploratory objectives.

Eligibility Criteria:

Adolescents and adults at least 12 years of age at the time of consent who have undergone first allogeneic hematopoietic stem cell transplantation (allo-HSCT) from any donor source using bone marrow, peripheral blood stem cells, or cord blood will be included in this study. Recipients of nonmyeloablative, reduced intensity, and myeloablative conditioning regimens are eligible. Patients must be diagnosed with SR-aGVHD. Steroid refractory (SR) is defined as aGVHD that progressed after 3 days of primary treatment with prednisone (or equivalent) of greater than or equal to 2 mg/kg/day; no improvement after 7 days of primary treatment with prednisone (or equivalent) of greater than or equal to 2 mg/kg/day; or previously was treated with prednisone (or equivalent) of greater than or equal to 1 mg/kg/day and aGVHD has developed in a previously uninvolved organ system. Patients with visceral (GI and/or liver) plus skin aGVHD at prednisone (or equivalent) initiation with improvement in skin GVHD without any improvement in visceral GVHD after 7 days of primary treatment with prednisone (or equivalent) of greater than or equal to 2 mg/kg/day are eligible. Patients must also have evidence of myeloid engraftment (e.g., absolute neutrophil count greater than or equal to 0.5×10^9/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation is allowed. Patients or an impartial witness (in case the patient is capable to provide verbal consent but not capable to sign the informed consent) should have given written informed consent.

	Exclusion Criteria: Patients will be excluded from study entry if any of the following exclusion criteria exist: Diagnosis of overlap syndrome, that is, with any concurrent features of cGVHD; patients requiring mechanical ventilation, requiring vasopressor support, or requiring hemodialysis; patients who have received any systemic treatment, besides steroids, as upfront treatment of aGVHD OR as treatment for SR-aGVHD; patients with severe hypoalbuminemia, with an albumin of less than or equal to 1 g/dl, a creatine kinase (CK) level greater than 5 times the upper limit of normal; patients with an uncontrolled infection (infections are considered controlled if appropriate therapy has been instituted and, at the time of enrollment, no signs of progression are present). Patients with evidence of relapsed, progressing, or persistent malignancy, or with evidence of minimal residual disease requiring withdrawal of systemic immune suppression are not eligible for this trial. Patients with known hypersensitivity to any of the components murine monoclonoal antibodies (mAb), or Recombinant Ricin Toxin A-chain (RTA), or have received more than one allo-HSCT, or who have known human immunodeficiency virus infection are also excluded from this trial. Pregnant or breastfeeding females, and females of childbearing potential unwilling to use effective birth control from start of treatment until 30 days after the last infusion of T-Guard are not eligible to participate. Male patients who are sexually active and unwilling to use effective birth control from start of treatment until 65 days after the last infusion of T-Guard are not eligible.
Interim Analysis:	This trial will include one interim analysis for futility after 21 patients become evaluable for the primary endpoint. There will be no interim analyses for efficacy.
Treatment Description:	Patients will receive 4 doses of T-Guard treatment, administered intravenously as four 4-hour infusions at least two calendar days apart. Each dose consists of 4 mg/m^2 Body Surface Area (BSA).
Accrual Objective:	The target accrual is 47 patients initiating T-Guard treatment.
Accrual Period:	Approximately 1 year is expected for accrual.
Study Duration:	Patients will be followed for 180 days for a total study duration of approximately 1.5 years.
Safety Monitoring:	The rates of overall mortality and CTCAE Grade 4 or higher capillary leak syndrome (CLS) at Day 30 post treatment initiation will be monitored separately using sequential probability ratio tests (SPRT) for binary data. The SPRTs will contrast a mortality rate of 15% vs. a 30% rate and a Grade 4 or higher CLS rate of 5% vs. a 15% rate.