PROTOCOL SYNOPSIS – BMT CTN 2002 PROTOCOL

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)

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Study Design: The study is an open-label, randomized, Phase 3, multicenter trial, which has been designed to compare the efficacy and safety of T-Guard to ruxolitinib in patients with Grade III or IV Steroid-Refractory acute Graft-Versus-Host Disease (SR-aGVHD).

The primary analysis will include all participants that are randomized.

Primary Objective: To assess the rate of complete response (CR) in Grades III and IV SR-aGVHD participants on Day 28 post-randomization.

Secondary Objectives: Secondary objectives are the following:

1. Estimate the overall survival (OS) at Days 60, 90, 180, and 365.
2. Evaluate the duration of complete response (DoCR).
3. Estimate the time to complete response (CR) from randomization.
4. Estimate the overall response rate (CR or partial response (PR)) at Days 14, 28, and 56.
5. Describe proportions of CR, PR, mixed response (MR), no response (NR), and progression of aGVHD at Days 6, 14, 28, and 56.
6. Estimate the cumulative incidence of non-relapse mortality (NRM) at Days 90, 180, and 365.
7. Estimate relapse-free survival at Days 180 and 365.
8. Estimate GVHD-free survival at Days 90, 180, and 365.
9. Estimate the cumulative incidence of chronic GVHD (cGVHD) at Days 180 and 365.
10. Estimate the cumulative incidence of underlying disease relapse/progression at Days 180 and 365.
11. Describe the incidence of infections.
12. Describe the incidence of adverse events.
13. Assess the pharmacokinetics (PK) of T-Guard.
14. Assess the immunogenicity of T-Guard.

Exploratory Objectives:

Exploratory objectives are the following:

1. Describe proportions of participants that are alive and free of systemic steroids at Days 90, 180, and 365 post-randomization.
2. Estimate the incidence of Cytomegalovirus (CMV) reactivation requiring therapy by Day 180 post-randomization.
3. Estimate the incidence of Epstein-Barr Virus (EBV)-associate lymphoproliferative disorder or EBV reactivation requiring therapy with rituximab by Day 180 post-randomization.
4. Evaluate the evolution and characteristics of specific cell populations at randomization and Days 0, 14, 56, and 180.
5. Evaluate aGVHD biomarkers at baseline and at Days 6, 14, and 28 post-randomization.
6. Describe changes in patient-reported outcomes (PROs) from baseline to Days 28, 90, and 180 post-randomization.
7. Estimate incidence of TMA at Days 6, 14, 21 and 28 post-randomization.
8. Describe EASIX score at aGVHD diagnosis.

Correlatives:

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

Eligibility Criteria:

Inclusion Criteria:

1. Patients must be at least 18.0 years of age at the time of consent.
2. Patient has undergone first allo-HSCT from any donor source or graft source. Recipients of nonmyeloablative, reduced intensity, and myeloablative conditioning regimens are eligible.
3. Patients diagnosed with Grade III or IV SR-aGVHD after allo-HSCT. SR includes aGVHD initially treated at a lower steroid dose, but must meet one of the following criteria:
    - progressed 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

- Patients who have skin GVHD alone and develop visceral aGVHD during treatment with methylprednisolone (or equivalent) of greater than or equal to 1mg/kg/day and do not improve after 3 days of greater than or equal to 2mg/kg/day

4. Patients must 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.
5. 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:

1. Patients who have a creatinine greater than or equal to 2mg/dL or estimated creatinine clearance less than 40 mL/min or those requiring hemodialysis.
2. Patients who have been diagnosed with active Thrombotic Microangiopathy (TMA), defined as meeting **all** the following criteria:
   - greater than 4% schistocytes in blood (or equivalent if semiquantitative scale is used e.g., 3+ or 4+ schistocytes on peripheral blood smear)
   - de novo, prolonged or progressive thrombocytopenia (platelet count less than 50 x 10^9/L or 50% or greater reduction from previous counts)
   - sudden and persistent increase in lactate dehydrogenase concentration greater than 2x ULN
   - decrease in hemoglobin concentration or increased transfusion requirement attributed to Coombs-negative hemolysis
   - decrease in serum haptoglobin
3. Patients who have previously received treatment with eculizumab.
4. Patients who have previously received checkpoint inhibitors (either before or after allo-HCT).
5. Patients who have been diagnosed with overlap syndrome, that is, with any concurrent features of cGVHD.
6. Patients requiring mechanical ventilation or vasopressor support.
7. Patients who have received any systemic treatment, besides steroids, as upfront treatment of aGVHD or as treatment for SR-aGVHD. Reinstitution of previously used GVHD prophylaxis agents (e.g., tacrolimus, cyclosporin, MTX, MMF) or substitutes in cases with previously documented intolerance will be permitted. Previous

treatment with a JAK inhibitor as part of GVHD prophylaxis or treatment is not allowed.

8. Patients who have severe hypoalbuminemia, with an albumin of less than or equal to 1 g/dL (10 g/L).
9. Patients who have a creatine kinase (CK) level of greater than 5 times the upper limit of normal.
10. Patients with uncontrolled infections. Infections are considered controlled if appropriate therapy has been instituted and, at the time of enrollment, no signs of progression are present. Persisting fever without other signs or symptoms will not be interpreted as progressing infection. Progression of infection is defined as:
    - hemodynamic instability attributable to sepsis OR
    - new symptoms attributable to infection OR
    - worsening physical signs attributable to infection OR
    - worsening radiographic findings attributable to infection
11. Patients with evidence of relapsed, progressing, or persistent malignancy, or who have been treated for relapse after transplant, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse.
12. Patients with evidence of minimal residual disease requiring withdrawal of systemic immune suppression.
13. Patients with unresolved serious toxicity or complications (other than acute GVHD) due to previous transplant.
14. History of sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD).
15. Patients with known hypersensitivity to any of the T-Guard components murine monoclonal antibodies (mAb) or recombinant Ricin Toxin A-chain (RTA) or known hypersensitivity to any of the components of ruxolitinib.
16. Patients who have had treatment with any other investigational agent, device, or procedure within 21 days (or 5 half-lives, whichever is greater) prior to enrollment. An investigational agent is defined as medications without any known FDA or EMA approved indications. Any prior and/or current participation in a clinical trial of an Investigational Medicinal Product (IMP) that is registered and being used off label requires review by the study's Protocol Officer, Protocol Chairs, and Sponsor prior to enrollment.
17. Patients who have received more than one allo-HSCT.
18. Patients with known human immunodeficiency virus infection or active hepatitis B infection.
19. Patients who have a BMI greater than or equal to 35 kg/m^2.

20. Patients who are taking sirolimus or everolimus **must** have it discontinued prior to starting study treatment.
21. Female patients who are pregnant, breast feeding, or, if sexually active and of childbearing potential, unwilling to use effective birth control from start of treatment until 30 days after the last treatment dose (see APPENDIX H).
22. Male patients who are, if sexually active and with a female partner of childbearing potential, unwilling to use effective birth control from start of treatment until 90 days after the last treatment dose (see APPENDIX H).
23. Patients with any condition that in the investigator's judgment would interfere with full participation in the study, including administration of study drug and attending required study visits (e.g., not able to swallow pills, mental instability), pose a significant risk to the patient, or interfere with interpretation of study data.
24. Patients whose decision to participate might be unduly influenced by perceived expectation of gain or harm by participation, such as patients in detention due to official or legal order.
25. Patients who have a platelet count less than 20 x 10^9/L despite transfusion, if any.

Interim Analysis: This trial will include one interim analysis for futility after 23 participants on the T-Guard arm (~46 participants total) become evaluable for the primary endpoint. One interim analysis for efficacy will be performed once 150 participants on combined arms have reached Day 28 and 100 participants on the combined arms have reached Day 180.

Treatment Description: Participants will be randomized to receive either T-Guard or ruxolitinib. Participants on the T-Guard arm 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). Participants on the ruxolitinib arm will receive 10mg orally of ruxolitinib twice daily for a planned minimal period of 56 days.

Accrual Objective: The target accrual is 246 participants randomized 1:1 between the treatment arms from approximately 75 transplant centers in the US and Europe.

Accrual Period: Approximately 34 months is expected for accrual.

Study Duration: Participants will be followed for 1 year after randomization for a total study duration of approximately 46 months.

Safety Monitoring: A safety run-in phase of 12 T-Guard participants (~24 on the combined treatment arms) will begin the trial, with two comprehensive safety reviews conducted by the DSMB after 6 and 12 T-Guard treated participants reach Day 30. The rates of early overall mortality post randomization will be monitored using sequential probability ratio tests (SPRT) for binary data. Two SPRTs will be implemented: one contrasting a Day 30 mortality rate of 15% vs. a 30% rate in the T-Guard arm specifically, and another evaluating whether excessive Day 60 mortality risk is present in the T-Guard arm compared to ruxolitinib.

Outline of Treatment Plan