BMT CTN 2002

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)

Indication:	Grade III or IV Steroid-Refractory Acute Graft-Versus-Host Disease (SR-aGVHD)
Developmental phase of study:	Phase 3
First participant enrolled:	16 June 2022
Last participant completed:	20 January 2023
Release date of report:	13 October 2023

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

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SIGNATURE OF SPONSOR APPROVAL

STUDY TITLE:
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)

SIGNATURE:
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Xenikos BV

DocuSigned by:
Ypke van Oosterhout
Signer Name: Ypke van Oosterhout
Signing Reason: I approve this document
Signing Time: 10/13/2023 | 11:39:39 AM CEST
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10/13/2023

Ypke van Oosterhout PhD
Founder and Chief Executive Officer
Xenikos BV

Date

SYNOPSIS

Name of Sponsor/Company: Xenikos

Name of Finished Product: T-Guard

Name of Active Ingredient:
T-Guard (immunotoxin combination consisting of equal amounts w/w of murine monoclonal antibodies [mAbs] dafsolimab (SPV-T3a: anti-CD3, IgG2b) and grisnilimab (WT1: anti-CD7, IgG2a), both individually conjugated to setaritox (Ricin Toxin A chain, RTA).

Title of Study: 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)

Organization and Sponsorship of the Study: the study was executed under the auspices of the Blood and Marrow Transplant Clinical Trials Network, which is founded and funded by the National Heart, Lung, and Blood Institute (NHLBI), and the National Cancer Institute (NCI), with the NHLBI as the lead institute. Xenikos BV operated as contributor to the study and was the formal study sponsor and holder of the Investigational New Drug Application (IND).

Principal Investigators: John Levine, MD, Gabrielle Meyers, MD, Gérard Socié, MD, Haris Ali, MD, Hannah Choe, MD, Andrew Harris, MD, Lia Perez, MD, Iskra Pusic, MD, Matthias Stelljes, MD, Walter Van der Velden, MD.

Study center(s): 9 (3 United States [US]; 6 Europe) out of 49 (12 US; 37 Europe) activated sites enrolled participants

Publications (reference): (Meyers et al. 2023)

Studied period (years):	**Phase of development:** 3
Date first participant enrolled: 16 June 2022 Date last participant completed: 20 January 2023	

Objectives:

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

Secondary:

1. Estimate the overall survival (OS) at Days 60, 90, and 180.
2. Evaluate the duration of complete response (DoCR).
3. Estimate the time to 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 and 180.
7. Estimate relapse-free survival at Day 180.
8. Estimate GVHD-free survival at Days 90 and 180.
9. Estimate the cumulative incidence of chronic GVHD (cGVHD) at Day 180.
10. Estimate the cumulative incidence of underlying disease relapse/progression at Day 180.
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.

Methodology: The study was an open-label, randomized, Phase 3, multicenter trial, which was designed to compare the efficacy and safety of T-Guard to ruxolitinib in participants with Grade III or IV SR-aGVHD. The study comprised 12 participants enrolled across 9 sites. The study enrolled participants who were at least 18 years of age, had undergone first allogeneic hematopoietic stem cell transplantation (allo-HSCT) from any donor source or graft source, and had received a diagnosis of Grade III or IV SR-aGVHD after HSCT and met all of the inclusion and exclusion criteria. Participants were randomized to receive either T-Guard or ruxolitinib. Participants were treated as soon as possible after enrollment, with a maximum of 72 hours permitted between enrollment and the start of treatment. Participants on the T-Guard arm were planned to receive 4 doses of T-Guard treatment, administered intravenously as four 4-hour infusions at least two calendar days apart. Each dose consisted of 4 mg/m^2 body surface area (BSA). Participants on the ruxolitinib arm received 10 mg orally of ruxolitinib twice daily for a planned minimal period of 56 days. Study assessments were planned to be conducted according to the protocol through Day 180 at the timepoints mentioned in the protocol; the timing of follow-up visits was based on the date of Randomization (Day 0).

Number of participants (planned and analyzed): A sample size of 246 participants was planned for this study with a 24-participant safety run-in. However, the study was stopped early after enrollment of 12 participants. All 12 participants consented and met inclusion criteria at enrollment. Of these participants, 7 were randomized to T-Guard and 5 to ruxolitinib treatment.

The primary analysis population comprised all participants randomized.

Diagnosis and main criteria for inclusion as defined in the protocols in effect at time of the patients being treated (US version 1.0, The Netherlands version 1.0, France version 1.3 and Germany version 1.1):

Inclusion Criteria:

1. Patients must be at least 18.0 years of age at the time of consent (for France: and should be registered into a social security system).
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. Steroid

refractory 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 2 mg/kg/day
- patients with visceral (gastrointestinal [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 2 mg/kg/day
- Patients who have skin GVHD alone and develop visceral aGVHD during treatment with methylprednisolone (or equivalent) of greater than or equal to 1 mg/kg/day and do not improve after 3 days of greater than or equal to 2 mg/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 (for France: Patients must be capable of reading and understanding the information sheet and informed consent form specific to the study and must have signed their written informed consent).

Exclusion Criteria:

1. Patients who have a creatinine greater than or equal to 2 mg/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 50×10^9/L or 50% or greater reduction from previous counts),
   - sudden and persistent increase in lactate dehydrogenase concentration greater than 2× upper limit of normal (ULN),
   - decrease in hemoglobin concentration or increased transfusion requirement attributed to Coombs-negative hemolysis, AND
   - 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-HSCT).
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, methotrexate [MTX], mycophenolate mofetil [MMF]) or substitutes in cases with previously documented intolerance will be permitted. Previous treatment with a Janus kinase (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.
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 components murine mAb or recombinant ricin toxin A-chain (RTA) (for France: 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.

17. Patients who have received more than one allo-HSCT
18. Patients with known human immunodeficiency virus infection
19. Patients who have a body mass index (BMI) greater than or equal to 35 kg/m^2
20. Patients who are taking sirolimus (for Germany: 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.
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 65 days (90 days for country amendment France) after the last treatment dose.
23. Patients with any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; 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 (this criterion was removed for France).
25. For France: Persons deprived of their liberty by judicial or administrative decision. Adults subject to a legal protection order (under some form of guardianship). Persons under safeguard measures.
26. For France: Patients who have a platelet count less than 20 × 10^9/L.

Test product, dose and mode of administration, batch number:

T-Guard, the test product, was administered as an IV infusion at 4 mg/m^2 over 4 hours every 2 calendar days for a maximum of 4 doses.

For participants >125% of their ideal bodyweight (IBW; calculated according to the Devine formula) the adjusted bodyweight (AWB) formula (IBW + 0.25 (ABW-IBW) was to be used to calculate BSA according to Mosteller:

$$BSA(m^2) = \sqrt{\frac{HEIGHT(cm) \times WEIGHT(kg)}{3600}}$$

The following drug product lot was used: B3017911.

Reference therapy, dose and mode of administration, batch number:

Ruxolitinib, the comparator, was administered as 10 mg orally twice daily.

The following drug product lots were used:

- Europe: SWA42, SDTN3, SDVP1 and SELR9
- US: 1848566

Duration of treatment:

T-Guard: 4 doses every 2 calendar days for a maximum of 4 doses and within a maximum of 14 days

Ruxolitinib: Minimal period of 56 days

Criteria for evaluation:

Efficacy:

The primary endpoint was the proportion of participants with a CR on Day 28 after randomization.

The key secondary endpoints were DoCR and OS.

- Duration of complete response was defined as the time from Day 28 until an aGVHD target organ worsens by at least 1 stage and requiring a significant escalation in treatment (defined below), or death. The transient worsening of symptoms that resolve without significant escalation of treatment was not considered a loss of CR. A significant escalation in treatment was defined as initiation of new systemic treatment for GVHD and/or escalation in methylprednisolone dose (or equivalent). Methylprednisolone dose increases must be greater than 25% of the current dose and increase at least 8 mg/day (or other steroid equivalent) to be considered an escalation of methylprednisolone. Duration of complete response was planned to be evaluated in the set of participants who are in CR on Day 28 after randomization.
- Overall survival was planned to be assessed at Days 60, 90, and 180 post-randomization. An event for this analysis is death from any cause and time will be calculated from randomization until date of death.

Other Secondary Endpoints were:

- Overall response rate (ORR) defined as having a CR or PR. The ORR will be estimated at Days 14, 28, and 56 post-randomization.
- Proportion of response: The proportion of participants in each aGVHD response category was planned be described at Days 6, 14, 28, and 56 post-randomization.
- Non-relapse mortality events included death from any cause other than relapse/progression of the underlying malignancy. Relapse was considered a competing risk.
- Time for NRM: determined by time of randomization until the earlier of death from a non-relapse cause or relapse (competing risk). Non-relapse mortality was estimated at Days 90 and 180 post-randomization.
- Relapse free survival (RFS): Events for RFS included death from any cause or relapse/progression of the underlying malignancy. Duration of RFS was calculated from randomization until the earlier of death or relapse/progression of the underlying malignancy. Relapse free survival was planned to be estimated at Day 180 post initiation of T-Guard.

- GVHD-free Survival: Participants alive with a CR and without cGVHD would have been considered a success for this endpoint. GVHD free survival was planned to be estimated at Days 90 and 180 post-randomization.
- Chronic GVHD was defined per National Institutes of Health Consensus Criteria. Time of cGVHD occurrence was planned to be calculated from randomization until the earlier of diagnosis of cGVHD or death from any cause, with death treated as a competing risk. The cumulative incidence of cGVHD at Day 180 post-randomization was planned to be estimated and maximum severity (mild/moderate/severe) was planned to be described.
- Relapse/progression of underlying malignancy: The cumulative incidence of malignancy relapse/progression was planned to be estimated with death prior to relapse/progression considered as a competing risk. The cumulative incidence of relapse/progression at Day 180 post-randomization was planned to be described.
- Incidence of Systemic Infections: All Grade 2 to 3 infections (as defined by Appendix G in the protocol) from randomization will be reported by site of disease, date of onset, and severity. Grade 1 cytomegalovirus (CMV) infections requiring treatment that occur post-randomization will also be reported. Incidence of systemic infections will be described in participants from randomization to 90 days post-randomization. The cumulative incidence of treated CMV post-randomization were planned to be described.
- Incidence of Toxicities: All Grade 3 to 5 toxicities according to Common Terminology Criteria for Adverse Events (CTCAE) occurring from randomization to 56 days post-randomization were planned to be described.
- Pharmacokinetics of T-Guard: A population PK model was planned to be developed for T-Guard based on the SPV-T3a- RTA and WT1-RTA levels measured in samples obtained before each infusion and at the following post-infusion timepoints: 4, 5, 6, 8, and 24 hours for the first infusion; 4, 6, and 24 hours for the second and third infusions; and 4, 6, 24, and 48 hours for the fourth infusion. The time points for blood sampling were based on the terminal half-life ($t_{1/2}$) and maximum concentration (C_{max}) values as determined in previous studies. The population PK model was planned to describe the following metrics:
  - C_{inf}: Observed and model-predicted concentration at the end of infusion
  - CL: Systemic clearance
  - AUC: Model-predicted area under the curve from the start of the current infusion until the next infusion or until 48 hours following for the last infusion
  - $t_{1/2}$: Model-predicted terminal half-life
  - Vc: Volume of the central compartment

  Additionally, the impact of various factors on these measures will be evaluated, including age, weight, BSA, BMI, disease status, and anti-drug antibodies (ADAs).
- Immunogenicity of T-Guard: Anti-drug antibody responses in the form of human anti-SPV-T3a-RTA and anti-WT1-RTA antibodies were planned to be evaluated in

serum samples obtained at baseline and at Days 6, 14, 28, 90, and 180 following initiation of treatment in T-Guard participants only.

Exploratory Endpoints:

- Discontinuation of Systemic Steroids: The proportion of participants that is free of systemic steroid therapy at Day 180 post-randomization was planned to be described.
- Incidence of CMV Reactivation: The proportion of participants requiring new systemic treatment for a CMV polymerase chain reaction level per institutional practice (participants receiving only standard of care viral prophylaxis were not included in this assessment) for CMV-reactivation by Day 180 post-randomization was planned to be described.
- Incidence of Epstein-Barr virus (EBV)-associated lymphoproliferative disorder: The proportions of participants with EBV-associated lymphoproliferative disorder and EBV reactivation requiring therapy with rituximab by Day 180 post-randomization was planned to be described.
- T-cell Subsets and natural killer (NK)-cells: The evolution and characterization of specific cell populations over the whole 180-day follow-up period was planned to be evaluated in both treatment arms in selected centers was planned to be evaluated. Samples of approximately 50 participants (25 T-Guard, 25 ruxolitinib) were planned to be taken at Days 0, 14, 28, 56, and 180 and either collected in CytoChex preservation tubes, or stored as viably frozen peripheral blood mononuclear cells (PBMCs), to allow for phenotypic and functional analysis of specific cell subsets, including e.g., flow cytometry and V-beta repertoire analysis. Flow cytometry analysis was planned to be included in the measurement of the following cell populations: inflammatory monocytes and dendritic cells, recent thymic emigrants, CD4+, CD8+ naïve and memory cells, CD4+ T regulatory cells, NK cells, γδ T cells, and B cells.
- GVHD-related biomarkers: graft versus host disease-related biomarker concentrations including serum interleukin 1 receptor-like 1 (ST2) and Regenerating Family Member 3 Alpha (REG3α) concentrations and urine 3-Indoxyl Sulfate (3-IS) concentrations at baseline and at Day 6, 14, and 28 post-randomization will be used to estimate the probability of NRM at Day 180 post-assessment for each participant, using the NRM risk model (Major-Monfried et al. 2018). The proportion of participants with high-risk biomarker status (defined as estimated NRM greater than 0.29) will be described at each time point.
- Patient reported outcomes were planned to be assessed using a subset of the PROMIS measures at baseline and Days 28, 90, and 180 post-randomization.
- Incidence of TMA: Incidence of TMA as defined in Section 2.4.2 in the protocol was planned to be assessed at Day 6, 14, 21, and 28 post-randomization. A blinded review panel was planned to review any participants that develop TMA criteria after randomization and treatment.
- Endothelial Activation and Stress Index (EASIX) Score: Endothelial Activation and Stress Index Score at time of screening was planned to be described.

Note that the above endpoints were defined in Protocol Version 1.0 while some revisions (i.e., protocol Version 2.1 was released to US sites on December 6, 2022) were never effectuated due to early study closure. As discussed in the Statistical Methods and Conclusions sections below, analyses in this study are limited to the primary endpoint and overall survival due to the early study closure. Other study endpoints are summarized via listings or were not analyzed.

Statistical Methods:

Analyses are mainly descriptive due to the early closure of the study and as such having only a data set of 12 participants. A limited set of endpoints are summarized via listings.

Serious adverse events (SAEs) were reported from the time of randomization until 30 days following the last dose of T-Guard and for the ruxolitinib arm through 44 days from randomization on the ruxolitinib arm to align with the maximum reporting period for participants in the T-Guard arm. In addition, any SAEs occurring after that period and assessed as related to the investigational product were to be reported. All SAEs were to be followed up until resolved, judged to be no longer clinically significant, or until they became chronic to the extent that they were fully characterized, including those ongoing at the time of death. Any unanticipated SAEs from the time of enrollment through the study defined follow-up were required to be reported. Infections, relapses, and GVHD events were collected separately as they were study endpoints. Should a Grade 2 to 3 infection have also met the SAE criteria, the infection was reported as an SAE per the established SAE reporting criteria. Grade 1 infections were not captured except for Grade 1 CMV infections, as defined in protocol Appendix G, requiring treatment were to be reported from randomization through the study defined follow-up period. The following adverse events of special interest were to be reported: any grade of 1) TMA, 2) CRS, 3) capillary leak syndrome, 4) myalgia, or 5) CK elevation and 6) grade 3 or higher cytopenias. These events were to be reported, regardless of grade (except for cytopenias grade 1 and 2) or seriousness, following the reporting process for SAEs. No statistical inference testing was performed on the safety data. All adverse events (AEs)/SAEs were coded using Medical Dictionary for Regulatory Activities Version 23.1.

Outcome-Summary:

Patient Population**:**

The study population consisted of 12 participants with Grade III and IV SR-aGVHD, who were recruited in Europe (n=9) and the US (n=3). Seven (7) participants were randomized to treatment with T-Guard and 5 participants were randomized to treatment with ruxolitinib. The two treatment groups were comparable with respect to gender, ethnicity, age, primary diagnosis, conditioning regimen, CMV status at transplant of the recipient and donor, human leukocyte antigen (HLA) match score, GVHD prophylaxis and SR-aGVHD grade.

The study was paused after enrollment of 12 patients because the 60 Day mortality stopping guideline was met. This triggered the Protocol Committee to ask for a post hoc assessment of five pre-existing risk factors for mortality to swiftly and easily determine a possible disbalance in risk profile at baseline between both treatment arms. This analysis pointed out that four factors were more prominent in the T-Guard arm than in the ruxolitinib arm: age ≥65 (3/7 vs 1/5, respectively), Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) >3 (3/3 vs 1/2; Note: missing data for 4 T-Guard and 3 ruxolitinib patients), serum albumin levels <2 g/dL (5/7 vs 2/5), and absolute neutrophil count (ANC) levels <1000/μL (1/7 vs 0/5).

Efficacy**:**

Primary and key secondary parameters:

CR Day 28 and DoCR: Two (2) out of 7 T-Guard treated participants (29%) achieved the primary outcome of CR at Day 28. Zero (0) out of 5 ruxolitinib treated participants (0%) were in complete remission at Day 28. The CR of 1 participant was durable until the last follow up date of the study (day 181). For the other participant the aGVHD progressed to stage 2 lower GI 35 days after start of treatment.

OS: Three (3) out of 7 T-Guard treated patients (43%) survived and 4 out of 5 (80%) of the ruxolitinib treated patients survived (survival sweep 24 March 2023).

Other secondary and exploratory parameters:

The Day 28 ORR was 57% and 60%, and the Day 56 ORR was 14% and 60% for the T-Guard and ruxolitinib treated participants, respectively.

The proportion of CRs on Day 56 was 14% for the T-Guard arm and 20% for the ruxolitinib arm. With regard to PR, the proportions at Day 28 were 29% and 60%, and on Day 56 were 0% and 40% for the T-Guard and ruxolitinib arm, respectively.

The NRM before Day 30, Day 60, Day 90, and Day 180 for the T-Guard treatment arm was 43% (3/7) and 57% (4/7) for Day 60 to Day 180, respectively. All deaths were assessed as unrelated to T-Guard by the treating physician. For the ruxolitinib treatment arm, the NRM before Day 30, Day 60, Day 90, and Day 180 was 0% (0/5) Day 30 to Day 120 and 20% (1/5) for Day 180.

None of the T-Guard treated patients reported symptoms of chronic GVHD. One participant in the ruxolitinib treatment group (20%) reported new symptoms of mild chronic GVHD, approximately 4 months after start of treatment.

No relapses of the underlying malignancy were reported.

Six infections were reported, which were equally divided over both treatment arms, translating to 43% (3/7) for the T-Guard treated and 60% (3/5) for ruxolitinib treated participants. For T-Guard, all 3 infections were assessed as Grade 2, for ruxolitinib the 3 infections were Grade 1, 2, and 3.

All other secondary and exploratory parameters (e.g., ADA, PK, PRO, GVHD biomarkers, and EASIX) were not analyzed due to the early closure of the study.

Safety**:**

All participants experienced AEs during the study that were consistent with underlying disease, complications of transplant, and treatment of SR-aGVHD.

A total of 70 AEs were reported in 11 participants, 39 AEs in 7 T-Guard- and 31 in 4 ruxolitinib treated participants. Most reported AEs were considered not related to study treatment by the Investigator (79% [26/33] and 93% [26/28] for T-Guard and ruxolitinib treated participants, respectively. The most prevalent event SOCs for T-Guard were Metabolism and nutrition disorders (27%; [9/33]), Blood and lymphatic system disorders (21%; [7/33]) and Investigations (18%; [6/33]), and for the ruxolitinib treated participants Gastrointestinal disorders (14%; [4/28]), Metabolism and nutrition disorders (14%; [4/28]) and Vascular disorders (11%; [3/28]).

For T-Guard, 3 AEs were considered possibly related (9% [3/33]: Grade 4 platelet count decreased and Grade 3 TMA (twice). One (1) AE (Grade 4 lymphocyte count decreased) was considered probably related (3% [1/33]). For ruxolitinib, 2 reported AEs (Grade 1 lipasemia and Grade 1 hyperbilirubinemia) were considered possibly related (7% [2/28]).

Nine (9) out of the 70 AEs were assessed as serious (6 in the T-Guard and 3 in the ruxolitinib treatment arm); one of them (Grade 4 respiratory failure) was considered possibly related to the study drug (in this case T-Guard).

Three (3) participants had treatment dose adjusted due to an AE: 2 participants (29% [2/7]) received only 2 out of 4 T-Guard doses due to Grade 3 TMA. For ruxolitinib, 1 participant (20% [1/5]) was lowered to 5 mg twice daily due to the occurrence of Grade 2 febrile neutropenia.

Discussion and Conclusion:

The currently reported randomized Phase 3 study (BMT CTN 2002) was developed in consultation with the Food and Drug Administration after closure of the single arm Phase 3 study (BMT CTN 1802) (Meyers et al. 2021, Meyers et al. 2023). The experience obtained in study BMT CTN 1802 was used to design the randomized BMT CTN 2002 trial by adding more stringent inclusion/exclusion criteria (e.g., screening for TMA, renal dysfunction and morbid BMI) and extra safety monitoring. A comparator arm randomized design was chosen to determine whether reported toxicities could be associated with investigational medicinal product treatment or were inherent to the very high-risk Grade III/IV SR-aGVHD population. Furthermore, staggered enrollment was implemented for the first 24 participants enrolled (safety run-in) to allow for continuous early mortality monitoring and an interim safety analysis before enrolling more participants.

Enrollment of the study started in June 2022. After enrollment of 12 participants, accrual of study BMT CTN 2002 was put on hold because the protocol-defined stopping boundary for Day 60 mortality was met (4 deaths in 7 participants in the T-Guard treatment arm vs0 deaths in 5 participants in the ruxolitinib treatment arm).

The primary cause of death for the T-Guard participants was GVHD in 3 of the 4 participants and infection in the fourth participant. This infection was considered related to GVHD too since it is a well-documented complication of transplant and SR-aGVHD. None of the deaths were assessed to be related to T-Guard as per Principal Investigator assessment.

The number, type, and prevalence of AEs and SAEs over the different treatment groups were as expected in this severely ill Grade III and IV SR-aGVHD population.

The Day 28 primary endpoint of CR was met in 2 out of 7 T-Guard treated participants and 0 out of 5 ruxolitinib participants.

Following review of the study data, the Data and Safety Monitoring Board (DSMB) recommended to terminate the study with the argument that despite the small number of participants enrolled, and the clinical setting of Grade III-IV SR-aGVHD, the incidence of mortality within the T-Guard arm was difficult to overlook and compelling. The DSMB discussed the previous study design for BMT CTN 1802 where the enrolled three participants all expired, and that the BMT CTN 2002 study was redesigned to minimize excess mortality with the same investigational product (IP). The NHLBI agreed with the recommendation of the DSMB, thereby formalizing the termination of the study which was executed under the auspices of the BMT CTN. No option was left for the Sponsor to appeal.

Xenikos, being the study Sponsor, respects the decision of the DSMB/NHLBI, but is of the opinion that there were no sound medical or statistical grounds for terminating the trial. This standpoint is further substantiated in Section 14 and boils down to the following points:

- The study population of BMT CTN 2002 had been changed to more severe patients with a higher risk of early mortality than its predecessor study BMT CTN 1802, i.e., from participants with Grade II-IV SR-aGVHD to those with Grade III-IV SR-aGVHD. The occurrence of early deaths was to be expected for this group of patients who were very sick at the time of enrollment.
- The causes of death were considered not being T-Guard related by the treating physicians and Medical Monitor of the Sponsor for all 4 T-Guard treated participants who died before Day 60.
- Due to the small sample sizes, no statistical evidence exists of a difference in mortality rate between the two treatment arms. This is further supported by a meta-analysis of the available Day 60 mortality data of Grade III-IV SR-aGVHD patients treated with T-Guard or with ruxolitinib, which analysis showed no notable difference in Day 60 mortality rate.
- Long term overall survival curves of the same Grade III-IV populations, show largely overlapping confidence intervals of the T-Guard and ruxolitinib patients, with a possible trend towards better overall survival of T-Guard treated patients starting at 2 months after treatment start. This is in line with the favorable Day 28 CR rate observed in T-Guard treated patients, which is considered a significant predictor of long-term overall survival in SR-aGVHD patients.

Given the above, the Sponsor is of the opinion that definitive conclusions regarding T-Guard's clinical safety and efficacy cannot be deduced from the 12 patients that had been randomized and treated in this study BMT CTN 2002, suggesting that the decision for early closure of the trial might have been premature.

Date of the report: 13 October 2023