CLINICAL OVERVIEW OF INFECTION EVENTS WITH ORCA-T VS CONVENTIONAL ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE PRECISION-T PHASE 3 STUDY

R. TAMARI[1], C. OLIAI[2], A. SALHOTRA[3], A. GANDHI[4], J. PANTIN[5], S. PATEL[6], R. HOEG[7], A. GOMEZ-ARTEAGA[8], R. FARAMAND[9], E. WALLER[10], S. KOSURI[11], A. JIMENEZ JIMENEZ[12], J. HOLTER-CHAKRABARTY[13], B. DHOLARIA[14], Y. CHEN[15], B. HAMILTON[16], J. MAGENAU[17], A. EGHTEDAR[18], A. PAVLOVA[19], J. McCLELLAN[19], N. FERNHOFF[19], R. NEGRIN[20], E. MEYER[20]

[1]Department of Medicine, Adult Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [3]Division of Leukemia, Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA, USA; [4]Center for Hematologic Malignancies - Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [5]Sarah Cannon Transplant and Cellular Therapy Program at TriStar Centennial Medical Center, HCA Healthcare, Nashville, TN, USA; [6]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA; [7]Comprehensive Cancer Center, University of California, Davis, Sacramento, CA, USA; [8]Weill Cornell Medicine, New York, NY, USA; [9]Blood and Marrow Transplantation and Cellular Immunotherapy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [10]Bone Marrow and Stem Cell Transplant Center, Emory University Winship Cancer Institute, Atlanta, GA, USA; [11]Hematology/Oncology, University of Chicago Medicine, Chicago, IL, USA; [12]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [13]OU Health Stephenson Cancer Center, Oklahoma City, OK, USA; [14]Department of Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, USA; [15]Hematopoietic Cell Transplant and Cell Therapy Program, Massachusetts General Hospital, Boston, MA, USA; [16]Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, OH, USA; [17]Rogel Cancer Center, University of Michigan, Ann Arbor, MI, USA; [18]Colorado Blood Cancer Institute, Denver, CO, USA; [19]Orca Bio, Menlo Park, CA, USA; [20]Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, Stanford, CA, USA

INTRODUCTION

- AlloHSCT can be curative for high-risk hematologic malignancies; however, infections remain a frequent and severe complication
- Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq (Orca-T) is a novel donor-derived allogeneic T-cell immunotherapy, leveraging high-purity regulatory T cells to induce immune tolerance through engineered graft composition
- The Precision-T Phase 3 study reported a 1-year estimated incidence of severe infections of 8.4% for Orca-T vs 16.1% for unmanipulated peripheral blood stem cells plus Tac/MTX (control arm)

AIM

- This exploratory analysis characterizes infection events in the Precision-T Phase 3 study (NCT05316701)

METHOD

- Adults (18–65 years) undergoing myeloablative alloHSCT for acute leukemia (intermediate or high DRI) in CR, or high-risk MDS (≤10% BM blasts), with HLA-matched (8/8) donors were randomized 1:1 to receive either Orca-T with single-agent Tac or unmanipulated PBSCs + Tac/MTX (control arm)
- Infection prophylaxis followed institutional practice; letermovir was required for CMV-seropositive participants. Infections were evaluated per BMT CTN Manual of Procedures by two reviewers
- The median follow-up was 11.4 months (range, 0.2–24.3)

CONCLUSIONS

- Severe infections with Orca-T were manageable and less frequent than in the control arm
- Prior work using T cell–depleted allografts identified a prognostic threshold of 50 CD4+ T cells/μL by D100 to define functional immune reconstitution; Orca-T reached median immune reconstitution above that level by D28
- Although the control arm had greater numbers of T cells in the months post-alloHSCT, Orca-T patients demonstrated a potential decrease in serious infection risk
- The cellular mechanism for accelerated functional immune responses observed with Orca-T may be due to:
  - Reduced pharmacological prophylaxis, which may improve T cell functional responses
  - Preclinical data showing that Tregs protect secondary lymphoid organs

RESULTS

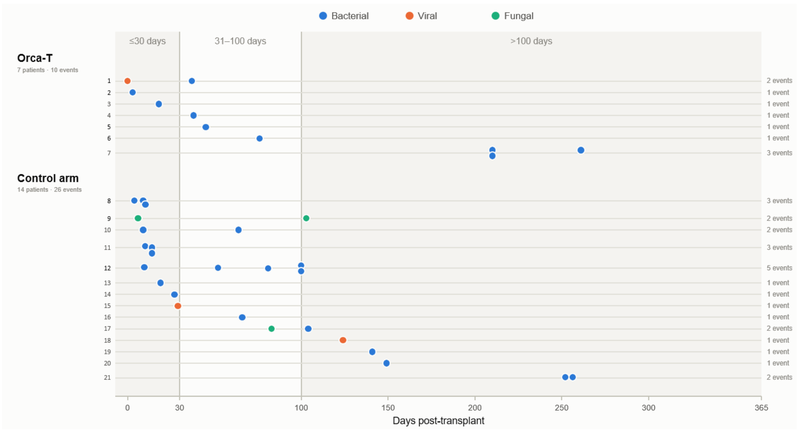

Figure 1. Patients with grade 3 BMT CTN MOP infection events by timepoint

- In Orca-T patients 8% (7/88) experienced grade 3 infections, with a total of 10 grade 3 events and in control arm patients, 15% (14/94) experienced a total of 26 grade 3 infections
- The increased rate of grade 3 infections in the control arm was attributed to a higher number of bacterial infections
- Median time to onset of bacterial infections was 76 days (range, 3–261) in the Orca-T arm and 52 days (range, 4–257) in the control arm
- Median duration of infection events was shorter with Orca-T: 12 days vs 16 days in the control arm
- In the Orca-T arm, 4 grade 3 infections and 10 events in the control arm had not resolved at time of data cut off
- Overall, the incidence of infections that resulted in ICU admissions was low; each arm had one patient admitted to ICU (control arm: pneumonia 4 days and Orca-T: sepsis 3 days)
- Viral reactivation was well controlled in both arms; 1 case of CMV reactivation in the Orca-T arm and 1 case of Epstein-Barr virus reactivation
- Two patients in the Orca-T arm and three patients in the control arm had infection as a cause of death

Infection event (Grade 3 by BMT CTN MOP)		Orca-T			Control		
		≤30 d	31–100 d	>100 d	≤30 d	31–100 d	>100 d
Bacterial	Sepsis, escherichia sepsis, septic shock, bacterial sepsis, enterococcal sepsis, staphylococcal sepsis	1	4	1	8	6	–
	Pneumonia, pneumonia aspiration, pneumonia klebsiella	–	–	3	2	–	2
	Other (nocardiosis, appendicitis, staphylococcal bacteremia, perirectal abscess)	1	–	–	–	1	2
Viral	Metapneumovirus pneumonia	1	–	–	–	–	–
	Cytomegalovirus colitis, Cytomegalovirus enterocolitis	–	–	–	1	–	1
Fungal	Fungaemia	–	–	–	1	1	1
Total events		3	4	4	12	8	6

Table 1. Infection Events by Timepoint. – Indicates no Events

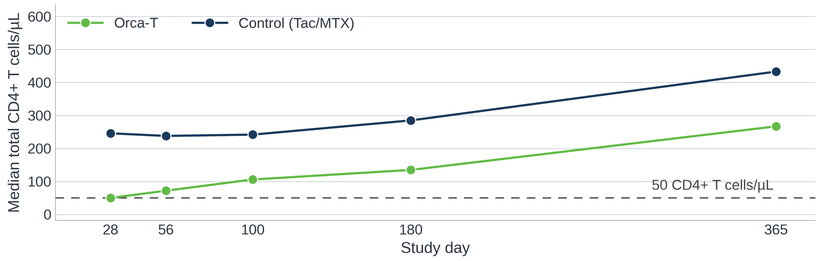

Figure 2. Immune Reconstitution: Median Total CD4+ Cell Counts

- In Orca-T, total T cell counts at D28 were lower (135/μL) as compared to the control arm (508/μL)
- CD4 T cell counts were 50/μL for Orca-T vs 246/μL for control arm at D28, with %Tregs of CD4 at 12% for Orca-T and 6% for control arm
- On both arms, CD4 + T-cell counts durably recovered to ≥50/μL by D28

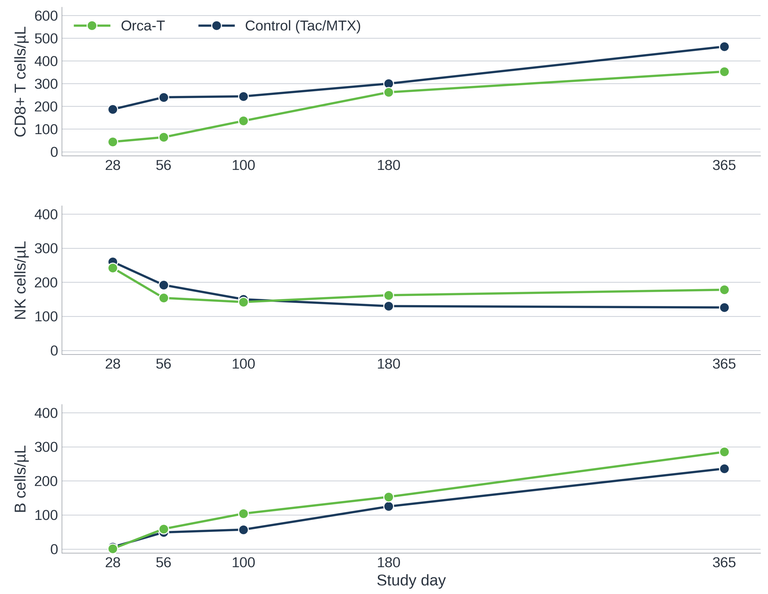

Figure 3. Immune Reconstitution: Median Total CD8+, NK, and B Cell Counts

- Rapid reconstitution of other immune cell populations was seen, including CD8+, NK, and B cells counts
- CD8+ T cell counts at D28 were 44/μL for Orca-T vs 187/μL for the control arm at D28

REFERENCES

Troullioud Lucas AG, Lindemans CA, Bhoopalan SV, et al. Early immune reconstitution as predictor for outcomes after allogeneic hematopoietic cell transplant; a tri-institutional analysis. *Cytotherapy.* 2023 Sep;25(9):977-985.

Meyer EH, Salhotra A, Gandhi AP, et al. Orca-T vs allogeneic hematopoietic stem cell transplantation (Precision-T): a multicenter, randomized phase 3 trial. *Blood.* 2026 Mar 12;147(11):1168-1177.