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Orca-T versus allogeneic hematopoietic stem cell transplantation (PRECISION-T): a multicenter, randomized phase 3 trial

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Abstract:
To prevent graft-versus-host disease (GVHD) in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation (alloHSCT), a calcineurin inhibitor plus methotrexate is routinely used. Early phase studies suggested improved outcomes with Orca-T, an allogeneic T-cell immunotherapy that uses purified donor Treg cells to prevent GVHD with significantly less immunosuppression. This phase 3 trial randomized adult patients (N=187) with acute leukemias or myelodysplastic syndrome undergoing myeloablative conditioning to receive either Orca-T with tacrolimus or a conventional allograft with tacrolimus and methotrexate (Tac/MTX), using granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood from HLA-matched donors. The primary endpoint was survival free from moderate-to-severe chronic GVHD (cGFS). Using a stratified log-rank test, cGFS was significantly higher in the Orca-T arm compared to Tac/MTX (P<0.001; HR 0.26; 95% CI, 0.14 to 0.47). One-year estimates were as follows: cGFS was 78.0% with Orca-T versus 38.4% with Tac/MTX; cumulative incidence of moderate-to-severe chronic GVHD (cGVHD) was 12.6% with Orca-T and 44.0% with Tac/MTX (Gray's test P<0.001), while overall survival (OS) was 93.9% with Orca-T versus 83.1% with Tac/MTX (P=0.12); GVHD and relapse-free survival (GRFS) was 63.1% and 30.9% in the Orca-T and Tac/MTX arms (P<0.001), respectively; non-relapse mortality (NRM) was 3.4% with Orca-T versus 13.2% with Tac/MTX (P=0.03). Orca-T met the primary endpoint of improved survival free from cGVHD compared to Tac/MTX prophylaxis and should be considered a new therapeutic option with low toxicity for GVHD prophylaxis. Additionally, significantly less toxicity was observed with Orca-T patients including fewer serious infectious complications and less non-relapse mortality. (ClinicalTrials.gov number NCT05316701).

Conflict of interest: COI declared - see note

COI notes: EM received clinical trial funding from Orca Bio and is named co-inventor of a patent owned by Stanford University and licensed to Orca with Robert Negrin. NBF, JSM, and JMM hold leadership positions and equity at Orca Bio. SK, AL, and AP declare employment and equity at Orca Bio. RF received consulting fees from Sanofi and travel support from Orca Bio to attend ASCO 2024 annual meeting. AS received research funding from BMS, Rigel and Orca Bio, consulting fees from Sanofi and support for speakers bureau participation from Sanofi and Incyte. AG received consulting fees from CareDx, support for speakers bureau participation from MJH Sciences, and panel participation at OncLive. She also received a travel grant from Orca Bio for oral presentation at EBMT 2025 annual conference. AJ received honorarium from the Saudi Society of Bone Marrow HCT and research funding from AbbVie. CO received research funding from Orca Bio, Electra Pharmaceuticals, Pfizer, Jazz Pharmaceuticals, Novartis, Ascentage, AstraZeneca, Takeda, Arog, Seagen, Syndax and Amgen. AGA received funding from the National Cord Blood Network, consulting fees from Kite Pharma, payment and honoraria from Sanofi and participated on an advisory board for Kite Pharma. BD received research grants from Janssen, Angiocrine, Pfizer, Poseida, MEI, Orca Bio, Wugen, Allovir, Adicet, BMS, Molecular Template, Atara and Merck. He also received consulting fees from MJH BioScience, Arivan Research, Janssen, ADC Therapeutics, Gilead, GSK, Caribou, Roche, Autolus, Poseida, AstraZeneca, travel support from Poseida, and has fiduciary role at NCCN and ASH. SP received support for speakers bureau participation from Kite Pharma and Sanofi, and is on the advisory board for CareDx. YC received consulting fees from Incyte, CSL Behring, MaaT Biotherapeutics, Ironwood, LifeMine, ProTGen, and Generation Bio, is on the trial committee for Novo Nordisk, Editas, Alexion and Daiichi, and received equity in ImmunoFree and Phesi. JP received compensation from Orca Bio for participation in advisory board post conclusion of the Precision-T Phase 3 trial. RN received consulting fees from Amgen, Garuda now StratusTherapeutics, Biorasi, Apia Bio, Cellenko, and ReStem. He was the inventor of an allogeneic transplantation patent that has been licensed to Orca Bio, served on the advisory/data safety monitoring board of Kura Oncology and University of Pennsylvania, is the Vice President and President Elect of American Society of Hematology, and received stock options from Garuda Therapeutics (now Stratus Therapeutics). BH received research funding from Incyte, payment from CSL Behring for educational video and from PeerView for attending and presenting at educational symposia. In addition, she is on the advisory board of Sanofi and Maat Pharma, on the adjudication committee of CSL Behring and on the DSMB committee of Angiocrine. JHC received a GVHD adjudication grant, support for attending American Society of Hematology (ASH) as executive board member and held leadership position at ASH, ASTCT, Access Initiative of ASTCT and NMDP and CIBMTR. SK (University of Chicago) received one-time payment from Sanofi and AbbVie for chronic GVHD and MDS lectures, respectively, and travel support from Sanofi for advisory board meeting. He is on the advisory board of Incyte and Sanofi, serves on the data and safety monitoring board of Cartesian Therapeutics, and is a member of BMT-CTN. RT, RH, AE, EKW have no interests to declare related to this study.

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Orca-T versus allogeneic hematopoietic stem cell transplantation (PRECISION-T): a multicenter, randomized phase 3 trial

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Key Points

In a randomized ph3 study, Orca-T significantly improved survival free cGVHD compared to conventional alloHSCT with Tac/MTX.

In addition to lower rates of cGVHD, Orca-T patients were also observed to have lower rates of acute GVHD, NRM, and serious infections.

Abstract

To prevent graft-versus-host disease (GVHD) in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation (alloHSCT), a calcineurin inhibitor plus methotrexate is routinely used. Early phase studies suggested improved outcomes with Orca-T, an allogeneic T-cell immunotherapy that uses purified donor Treg cells to prevent GVHD with significantly less immunosuppression. This phase 3 trial randomized adult patients (N=187) with acute leukemias or myelodysplastic syndrome undergoing myeloablative conditioning to receive either Orca-T with tacrolimus or a conventional allograft with tacrolimus and methotrexate (Tac/MTX), using granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood from HLA-matched donors. The primary endpoint was survival free from moderate-to-severe chronic GVHD (cGFS). Using a stratified log-rank test, cGFS was significantly higher in the Orca-T arm compared to Tac/MTX (P<0.001; HR 0.26; 95% CI, 0.14 to 0.47). One-year estimates were as follows: cGFS was 78.0% with Orca-T versus 38.4% with Tac/MTX; cumulative incidence of moderate-to-severe chronic GVHD (cGVHD) was 12.6% with Orca-T and 44.0% with Tac/MTX (Gray's test P<0.001), while overall survival (OS) was 93.9% with Orca-T versus 83.1% with Tac/MTX (P=0.12); GVHD and relapse-free survival (GRFS) was 63.1% and 30.9% in the Orca-T and Tac/MTX arms (P<0.001), respectively; non-relapse mortality (NRM) was 3.4% with Orca-T versus 13.2% with Tac/MTX (P=0.03). Orca-T met the primary

endpoint of improved survival free from cGVHD compared to Tac/MTX prophylaxis and should be considered a new therapeutic option with low toxicity for GVHD prophylaxis. Additionally, significantly less toxicity was observed with Orca-T patients including fewer serious infectious complications and less non-relapse mortality. (ClinicalTrials.gov number NCT05316701).

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHSCT) permanently replaces the diseased blood and immune system in a patient with that of a healthy donor. It is the only potentially curative therapy for many benign blood disorders and high-risk hematological malignancies.[1] However, the use of alloHSCT is limited by graft-versus-host disease (GVHD), a sustained immune reaction initiated by the donor T cells against the recipient's normal healthy tissues, commonly liver, skin, gastrointestinal tract, and lungs.[2] Despite multi-agent immune suppression, GVHD remains a major complication following alloHSCT. Furthermore, the pharmacological agents used to prevent GVHD are a source of secondary complications. Therapy-related toxicities ultimately limit the application of alloHSCT to high-risk hematological malignancies and bone marrow failure disorders.

For the past thirty years, GVHD prophylaxis approaches have been developed that deplete donor T lymphocytes either *ex vivo* using graft engineering) or *in vivo* using post-transplant cyclophosphamide (PTCy) or anti-thymocyte globulin (ATG). However, the benefit of superior GVHD control of these strategies has been offset by the delayed immune reconstitution, increased infectious complications, and excess NRM.[3,4] These studies underscore the dual actions of donor T cells to (i) therapeutically reconstitute the immune system to provide graft versus leukemia (GvL) and graft versus infection (GvI) and to (ii) pathogenically react against normal tissue to cause GVHD. Therefore, improvements in alloHSCT outcomes will require strategies that selectively control T cell function to maintain immune reconstitution and prevent GVHD.

In preclinical models of alloHSCT, donor-derived, polyclonal CD4+CD25+FoxP3+ regulatory T cells (Tregs) were shown to modulate T-cell alloreactivity to mitigate GVHD, maintain GvL[5,6] and promote immune reconstitution.[7] This concept has been translated in single-institution clinical studies with haploidentical transplantation[8,9], with expanded umbilical cord blood cells[10] and with matched donor-derived PBSCs.[11,12] However, the complexity of graft engineering has, until now, prevented the translation of single center efforts to general clinical practice.

Orca-T is an allogeneic T-cell immunotherapy, produced and distributed from a central GMP facility, that consists of individually formulated (i) hematopoietic stem and progenitor cells (HSPCs), (ii) high-purity Tregs, and (iii) conventional T cells (Tcons). In early phase studies, Orca-T recipients demonstrated high survival rates and low rates of acute and chronic GVHD, infection, and NRM.[12,13] Here, we present the efficacy, safety and immune reconstitution outcomes from a randomized phase 3 study of Orca-T compared to conventional alloHSCT conducted at 19 centers across the United States.

Methods

Trial design

This randomized, multicenter phase 3 trial compared Orca-T with single-agent tacrolimus to a control arm comprised of a PBSC allograft with tacrolimus and methotrexate (Tac/MTX) in patients with acute leukemia or myelodysplastic syndrome (MDS) who received myeloablative conditioning (Figure 1). The primary objective was to compare rates of survival free from moderate-to-severe chronic GVHD (cGFS) in the two arms using a time-to-event analysis, with an event being defined as the development of moderate-to-severe chronic GVHD or death from any cause. The primary analysis of cGFS was pre-specified to be conducted at the 56th event. For the primary analysis, chronic GVHD was assessed by an independent endpoint adjudication committee (EAC) blinded to treatment arm assignment. The Sponsor was blinded to aggregate study results; treatment assignment was known to clinical sites, patients, and treating physicians.

The protocol, available with the full text of this article at the *Blood* website, was approved by the institutional review board (IRB) of each participating center, and all the patients and donors provided written informed consent. The trial

was funded by Orca Bio. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

Patients

Patients aged 18 to 65 years of age who planned to undergo their first alloHSCT from an HLA matched donor after myeloablative conditioning were enrolled into the study. Eligibility included acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or mixed phenotype acute leukemia (MPAL) in complete remission (CR) or complete remission with incomplete count recovery (CRi), or myelodysplastic syndrome (MDS) with no circulating blasts and fewer than 10% blasts in the bone marrow. Eligible patients had adequate organ function, hematopoietic cell transplantation-specific comorbidity index[14] (HCT-CI) ≤4, and were classified as disease risk index (DRI) category intermediate or high.[15] All donors, related and unrelated, were 8/8 matched at HLA-A, HLA-B, HLA-C, and HLA-DRB1 alleles by high resolution DNA-based typing.

Treatment

Myeloablative conditioning regimens included either (i) fludarabine (160 mg per square meter of body-surface area), thiotepa (10 mg per kilogram), and busulfan [intravenous, 9.6 mg per kilogram or dosed to maintain an average daily area under the curve of 4,800-6,000 μM-min (19.7 – 24.6 mg*H/L)], (ii) etoposide (60 mg per kilogram) and total-body irradiation (1200 – 1320 cGy), or (iii) cyclophosphamide (100 – 120 mg per kilogram) and total-body irradiation (1200 – 1420 cGy).

For both arms, PBSCs were mobilized in donors via G-CSF stimulation over 5 days and collected via apheresis. For each Orca-T recipient, PBSCs were couriered by Orca Bio (related donors) or the National Marrow Donor Program (NMDP, unrelated donors) to Orca Bio's GMP central manufacturing facility (Sacramento, CA) where cellular infusions were purified and formulated. HSPCs and Treg infusions were on day +0, and Tcon infusion was on day +2 or +3. Tacrolimus was initiated on the day following Tcon infusion (Figure S1). For Tac/MTX recipients, PBSCs were obtained locally (related donors) or couriered by NMDP (unrelated donors). The unmanipulated allograft was infused on day +0 and tacrolimus was initiated on day -3. Methotrexate was administered at doses of 15 mg per square meter of body-surface area IV bolus on day +1, and 10 mg per square meter of body-surface area IV bolus on days +3, +6, and +11 (Figure S1).

Tacrolimus dosing and tapering was the same for both arms: initiated at 0.03 mg/kg/day IV, with a target trough blood level of 5 to 10 ng/mL and taper initiated ≥90 days after HSCT in the absence of active GVHD, reduced approximately 20% per month. Post-transplant, targeted maintenance therapies (FLT3, IDH, or BCR-ABL inhibitors) were allowed on study, Additional medical management is described in the clinical protocol. First-line acute GVHD treatment was also the same for both arms. Letermovir prophylaxis was mandated for cytomegalovirus (CMV)-seropositive recipients.

Endpoints

The primary endpoint for this phase 3 Precision-T study was cGFS, a time-to-event outcome defined as the time from transplantation (day 0) to either death from any cause or the onset of moderate-to-severe chronic GVHD per the 2014 NIH consensus criteria.[16] All patients were assessed for the presence or absence of chronic GVHD by a blinded end-point adjudication committee (EAC) comprised of independent physicians not participating on the study who were given access to primary patient data. The EAC assigned organ specific severity scores for GVHD. Secondary endpoints were time to moderate-to-severe chronic GVHD, overall survival (OS), and GVHD- and relapse-free survival (GRFS), with the latter measuring the earliest of death, relapse, grade 3 or 4 acute GVHD[17], or moderate-to-severe chronic GVHD. Exploratory endpoints included hematopoietic reconstitution, acute GVHD, infections, NRM, and relapse-free survival (RFS).

Statistical analysis

The complete Statistical Analysis Plan (SAP) is provided in the supplementary materials. Patients were assigned treatment using dynamic block randomization in a 1:1 ratio to the Orca-T arm or to the Tac/MTX arm, stratified according to donor type (matched sibling donor or matched unrelated donor) and the disease risk index (intermediate or high). The primary analysis was conducted at 56 total events (moderate-to-severe chronic GVHD or death), the number of events required to achieve 90% power with a true hazard ratio of 0.40 and an overall alpha of 0.05 with two-sided testing. A minimum enrollment of 165 patients was calculated, but 187 patients were ultimately

randomized to account for potential early study discontinuations. Secondary endpoints were tested hierarchically in the following sequence only if the primary endpoint and all preceding endpoints were significant: time to moderate-to-severe cGVHD per EAC, OS, and GRFS. This study was not powered for any of the secondary endpoints. The intention-to-treat (ITT; i.e. as randomized) populations were considered for primary and secondary endpoints. Exploratory endpoints included RFS, NRM, acute GVHD, chronic GVHD (all-grade), relapse, and engraftment. The safety populations (i.e, as treated) were evaluated for these exploratory endpoints.

Here, we report the results of primary analysis for cGFS and chronic GVHD. For cGFS, a two-sided alpha of 0.0116 was spent at interim analysis, with 0.0464 remaining for the primary analysis. Interim results for OS and GRFS are presented here; a primary analysis of these outcomes is planned for a later time. All the secondary endpoints were to apply a generalized Haybittle–Peto boundary with a two-sided alpha of 0.05 remaining for their corresponding primary analyses.

In the primary analysis for cGFS, a 2-sided log-rank test, stratified by the randomization variables (i.e., donor type and DRI; hereafter referred to as 'RV-adjusted'), with a significance threshold of 0.0464 was used to test the null hypothesis of no treatment effect with respect to cGFS. In addition, the HR with a 95% CI was estimated from an RV-adjusted Cox regression model. The same analytic approaches were used for OS and GRFS. For time to moderate or severe chronic GVHD where death was considered a competing event, and NRM where relapse was considered a competing event, the P values for the hypotheses tests were calculated from RV-adjusted Gray's tests, and RV-adjusted sub-distribution proportional hazards models were used to calculate treatment HRs with 95% CIs. Additional details of exploratory analyses are included in the Supplementary Appendix and SAP.

Role of the funding source

Orca Bio was the funder of the study and Orca Bio authors had a role in study design, data collection, data analysis, data interpretation, writing of the report, and submission of this manuscript.

Results

Patients

Between June 25, 2022, and June 18, 2024, a total of 187 patients at 19 centers in the United States were enrolled in the trial (Table 1, Figure S2 and Table S1 in Supplementary Appendix, available at the *Blood* website). The CONSORT diagram shows the flow of patients during screening, randomization, treatment, and follow-up (Figure 1). Salient patient characteristics at the time of transplantation are shown in Table S2. Of the 94 patients randomized to the Tac/MTX arm, 93 received an 8/8 HLA matched alloHSCT, while one received a haploidentical allograft with post-transplant cyclophosphamide-based prophylaxis due to drop out of the original matched donor. All 4 doses of MTX were administered for 82 (87%) Tac/MTX patients, 10 (11%) missed at least one MTX dose due to toxicity, and complete MTX dosing information was not available for 2 (2%) patients. Five of 93 patients randomized to the Orca-T arm had not received Orca-T at the time of data cutoff: two withdrew consent prior to treatment, two relapsed before treatment (one who eventually received Orca-T after the primary analysis), and one had delayed treatment due to SARS-CoV-2 infection and instead received a cryopreserved PBSC allograft plus Tac/MTX. All remaining 88 Orca-T patients received an Orca-T product within 72 hours of donor apheresis. Orca-T product characteristics are provided in Figure S3. The database lock took place on January 8, 2025, for the primary analysis. Patient variables were well-balanced across the two study arms, and patients enrolled in this trial were representative of the general alloHSCT population (Table 1 and Table S3). The median follow-up was 11.4 months (range 0.2 - 24.3 months) at the database lock date.

Primary endpoint

A total of 58 events (death or moderate-to-severe chronic GVHD) occurred in the ITT population: 14 in the Orca-T arm and 44 in the Tac/MTX arm. A multivariate Cox regression model showed a hazard ratio of 0.26 (95% CI, 0.14 to 0.47; P<0.001). One-year estimated survival free from moderate-to-severe chronic GVHD (cGFS) was 78.0% (95% CI, 65.0% to 86.6%) for Orca-T and 38.4% (95% CI, 26.2% to 50.5%) for Tac/MTX (Figure 2A). Orca-T exhibited higher cGFS across all subgroups in pre-specified sensitivity analyses (Figure S4).

Secondary endpoints

The secondary endpoints were evaluated hierarchically as described above (see Methods). First, moderate-to-severe chronic GVHD was significantly reduced for the Orca-T arm versus the Tac/MTX arm (HR 0.19, P<0.001). The one-year estimated cumulative incidence of moderate-to-severe chronic GVHD for Orca-T was 12.6% (95% CI, 5.3% to 23.1%) versus 44.0% (95% CI, 31.3% to 56.1%) for Tac/MTX (Figure 2B). Overall, 7 total Orca-T treated patients developed moderate (n=6) or severe (n=1) chronic GVHD. In comparison, 30 total Tac/MTX treated patients developed moderate (n=18) or severe (n=12) chronic GVHD. Organ systems affected by chronic GVHD in each arm are shown in Figure S5A, and systemic therapies used to treat patients who developed cGVHD in each arm are shown in Figure S5B.

Second, one-year estimated OS was 93.9% (95% CI, 85.8% to 97.4%) for Orca-T patients versus 83.1% (95% CI, 72.9% to 89.8%) for Tac/MTX patients (HR 0.49, P=0.12) (Figure 2C). Lastly, one-year estimated GRFS was 63.1% (95% CI, 50.0% to 73.6%) for Orca-T versus 30.9% (95% CI, 20.0% to 42.4%) for Tac/MTX (HR 0.37; 95% CI, 0.23 to 0.60; P<0.001) (Figure 2D). Because the interim OS analysis did not cross the alpha-controlled boundary, GRFS is reported descriptively with no formal claim of significance. Primary analyses for OS and GRFS endpoints are forthcoming per SAP.

Other major treatment outcomes

The as-treated populations were analyzed for other study outcomes (Table 2). No patients experienced primary graft failure, and neutrophil engraftment was similar between the two arms (median 13 days with Orca-T versus 14 days with Tac/MTX) (Figure S7). Platelet engraftment was also similar between the two arms (median, 17 days for Orca-T and 18 days for Tac/MTX), and delayed platelet engraftment was noted for one Orca-T patient and two Tac/MTX patients (Figure S7). One Orca-T patient had secondary graft loss. Grade II acute GVHD was similar across both treatments, but the cumulative incidence for grade III or IV acute GVHD at day +180 was 6.2% (95% CI, 2.3 to 12.9) with Orca-T versus 16.5% (95% CI, 9.4 to 25.3) in the Tac/MTX arm (HR 0.37 (95% CI, 0.13 to 1.02); P=0.044) (Table 2). One-year cumulative incidence of any grade chronic GVHD per investigator assessment was 21.9% (95% CI, 11.7 to 34.2) with Orca-T versus 67.5% (95% CI, 53.9 to 77.9) with Tac/MTX, corresponding to a preventable fraction of 67.6%. Estimated one-year relapse-free survival was 75.5% (95% CI, 63.0 to 84.3) for Orca-T and 74.1% (95% CI, 62.7 to 82.5) for Tac/MTX (HR 0.80, P=0.49) (Table 2). Cumulative incidence of relapse or progression at one year was 21.1% (95% CI, 11.9 to 32.0) for Orca-T and 12.7% for Tac/MTX (95% CI, 6.4 to 21.4) (P=0.33). Furthermore, the cumulative incidence of non-relapse mortality (NRM) at one year was 3.4% (95% CI, 0.9% to 8.8%) for Orca-T versus 13.2% (95% CI, 6.8% to 21.6%) for Tac/MTX (HR 0.27 (95% CI, 0.08 to 0.93); P=0.03) (Table 2). The reduced NRM with Orca-T was due to fewer deaths from organ toxicity, GVHD, and infection (Figure 3D).

On both arms, CD4+ T cell counts durably recovered to ≥ 50 μL by day +28 (Figure 3A) with rapid reconstitution of other immune cell populations as well (Table S4).[18] Tregs were proportionally more abundant among CD4+ T cells in Orca-T patients during early immune reconstitution and remain elevated relative to Tac/MTX patients through day +180 (p<0.05) (Figure 3B and Table S4). Both arms achieved full donor granulocyte chimerism by day +28, and median T cell chimerism levels at day +28 were 86% and 95%, for Orca-T and Tac/MTX respectively (Figure S7A). Some Orca-T patients required a longer time to achieve full donor T-cell chimerism, but mixed T-cell chimerism did not predict relapse with Orca-T at any timepoint in the first year post transplant (Figure S7B).

Infectious complications were evaluated using the BMT CTN Manual of Procedures (MOP) scoring.[19] Grade 2+ infections were similar between the two arms, but grade 3+ infections were less common with Orca-T (Table 2). There were 10 Grade 3 infections among 7 Orca-T patients and 26 Grade 3 infections among 14 Tac/MTX patients. One-year estimated incidence of grade 3 infections was 8.4% (95%CI, 3.6% to 16%) for Orca-T versus 16.1% (95% CI, 9.2% to 25%) for Tac/MTX (Figure 3C). CMV and Epstein-Barr virus (EBV) were equally well-controlled in both arms, with one case of CMV reactivation in the Orca-T arm and one case of EBV reactivation in each study arm.

Safety events observed between the two arms are noted in Table 2, Table S5, Table S6, and the Supplementary Appendix text. Serious treatment-emergent adverse events (TEAEs) developed in 38.6% of Orca-T patients versus 56.4% of Tac/MTX patients. Hospital readmissions after initial discharge for alloHSCT were 27.3% for Orca-T patients versus 45.7% for Tac/MTX patients (Table 2).

Discussion

In this randomized, phase 3 trial of patients with acute leukemia or MDS undergoing alloHSCT with myeloablative conditioning using HLA-matched donors, Orca-T with single-agent tacrolimus met the primary endpoint of improved survival free from moderate-to-severe chronic GVHD compared to a conventional allograft with Tac/MTX. The improvement was due to a significant reduction in moderate-to-severe chronic GVHD and fewer patient deaths. In addition, patients treated with Orca-T also experienced lower rates of acute GVHD, fewer serious infections, less rehospitalization, and less NRM.

The Orca-T design builds directly on the foundation of prior graft engineering efforts. The landmark BMT CTN 1301 study prospectively randomized patients to one of three arms: (i) a T-cell depleted allograft without pharmacological prophylaxis, (ii) a T-cell replete bone marrow allograft with Tac/MTX, or (iii) a T-cell replete bone marrow allograft with PTCy.[4] T-cell depletion significantly reduced the incidence of chronic GVHD relative to the other arms; however, it also increased the rates of serious infections, NRM, and OS. In Orca-T, the intended use of Treg and Tcon components is to provide GVHD control and rapid immune function, respectively. In the present study, Orca-T patients rapidly reconstituted conventional T cells, including CD4+ T cells, and their rates of serious infections were correspondingly low. In conjunction, the relative proportion of regulatory T cells during immune reconstitution was elevated, while the rates of GVHD were low. These results highlight a consistent mechanism of action where precise control of donor Tregs and Tcon compositions orchestrate a balanced immune reconstitution that leads to a therapeutic effect.

Conventional allografts contain high concentrations of donor T cells, typically >100 million per kilogram[20] and require multi-agent GVHD prophylaxis. In contrast, a T-cell depleted allograft generally contains less than 50 thousand T cells per kilogram and rarely requires any pharmacological immune suppression. Adaptations that add back a limited dose of donor T cells to a T-cell depleted allograft have been investigated, but were unable to identify a dose that was able to both prevent GVHD and promote rapid immune reconstitution.[21] A fundamental discovery in murine models of alloHSCT showed that donor Tregs were capable of controlling the alloreactivity of donor T cells without compromising immune function or disease relapse.[6,7] This activity was substantially augmented when pure Tregs were delivered two days prior to Tcon which exploits alloreactive proliferation of Treg and a suppressive reaction against recipient dendritic cells in secondary lymphoid organs.[22–24] The Treg:Tcon addback strategies were translated to clinical trials first by the Perugia group and then others with promising reductions in GVHD.[8,9,11,12] However, the complexity of graft engineering has been difficult to scale to routine clinical use, even at transplant centers with sophisticated cell manufacturing capabilities. Orca-T addresses this barrier via a central manufacturing and distribution platform. The cellular infusions of Orca-T are quality controlled to meet dose, purity, potency, and safety specifications. In this phase 3 study, all batches of Orca-T were manufactured, distributed to clinical sites, and infused within a 72-hour vein-to-vein timespan. Accordingly, Orca-T translates decades of graft-engineering research into a widely available immune cell therapy.

This study had certain limitations. In earlier trials, Orca-T exhibited a potential synergy when combined with a busulfan/fludarabine/thiotepa (BFT) conditioning regimen. Therefore, to reduce heterogeneity and to isolate the treatment effect of Orca-T, the myeloablative regimens in this study protocol were restricted, preventing a broader assessment of generally used conditioning agents. BFT is an intensive conditioning regimen that reduces relapse, although at the expense of higher NRM.[25,26] Patients in the Tac/MTX arm of this study which used BFT experienced lower rates of relapse and higher rates of NRM when compared to Tac/MTX arm in BMT CTN 1301 which used Bu/Cy and Bu/Flu conditioning.[4] This context is important as the relapse rates with Orca-T remain consistent with expectation for this patient population, while the exceptionally low NRM and high rates of OS demonstrates the potential of Orca-T to improve safety without compromising efficacy. Next, this study employed Tac/MTX prophylaxis in a single control arm. With regards to GVHD, ATG has demonstrated superiority over Tac/MTX in randomized studies that have informed European practice.[27,28] Randomized studies of alloHSCT in the US and Australia with HLA-matched donors in the reduced intensity context have recently demonstrated superior GVHD control with PTCy-based regimen compared to Tac/MTX.[29] However, no multicenter, randomized study has shown clear superiority of this patient population in the myeloablative setting.[30] Currently, both PTCy and ATG are commonly used GVHD prophylaxis in clinical practice, but delayed immune reconstitution, infection, and NRM remain frequently reported complications. A retrospective comparison of Orca-T patients treated in the Phase 1b trial to a historical registry cohort of PTCy patients showed promising improvements in overall survival with Orca-T

over 3 years[31], but a prospective randomized trial against PTCy or ATG may be needed for a more definitive assessment of outcomes.

In conclusion, patients who received Orca-T and single-agent tacrolimus had superior survival free from GVHD compared to those who received a PBSC allograft and Tac/MTX, owing to both fewer cases of GVHD and fewer deaths. Orca-T provided improved outcomes with less immune suppression, and these results establish Orca-T as a new therapeutic option for patients with hematological malignancies. These results also mark the first demonstration of efficacy with a Treg-based immunotherapy. Finally, the low NRM rate and favorable safety profile of Orca-T merits further investigation in patients with other hematological, genetic, and autoimmune disorders where conventional alloHSCT has demonstrated efficacy but utilization remains limited due to high NRM and other toxicities.

Contributors

NF, EM and JSM prepared the first draft of the report after discussions with all authors about the results. All authors participated in the subsequent drafting, critical revision and approval of the manuscript. NF and JSM conducted literature searches and accessed and verified the data. EM, JSM, NF, RN, and AP were involved in conceptualization, study design, data analysis and interpretation of data. EM, AS, AG, JP, SP, RH, AGA, RF, RT, EW, SK, AJ, JHC, BD, YC, BH, JM, AE and CO were clinical investigators in the study and participated in data interpretation, critical review, editing and proofreading of the manuscript. AL and SK conducted statistical analysis of clinical endpoints and exploratory data and generated figures and tables. EM, NF and JSM were responsible for the decision to submit the manuscript.

Declaration of interests

EM received clinical trial funding from Orca Bio and is named co-inventor of a patent owned by Stanford University and licensed to Orca with Robert Negrin. NBF, JSM, and JMM hold leadership positions and equity at Orca Bio. SK, AL, and AP declare employment and equity at Orca Bio. RF received consulting fees from Sanofi and travel support from Orca Bio to attend ASCO 2024 annual meeting. AS received research funding from BMS, Rigel and Orca Bio, consulting fees from Sanofi and support for speakers bureau participation from Sanofi and Incyte. AG received consulting fees from CareDx, support for speakers bureau participation from MJH Sciences, and panel participation at OncLive. She also received a travel grant from Orca Bio for oral presentation at EBMT 2025 annual conference. AJ received honorarium from the Saudi Society of Bone Marrow HCT and research funding from AbbVie. CO received research funding from Orca Bio, Electra Pharmaceuticals, Pfizer, Jazz Pharmaceuticals, Novartis, Ascentage, AstraZeneca, Takeda, Arog, Seagen, Syndax and Amgen. AGA received funding from the National Cord Blood Network, consulting fees from Kite Pharma, payment and honoraria from Sanofi and participated on an advisory board for Kite Pharma. BD received research grants from Janssen, Angiocrine, Pfizer, Poseida, MEI, Orca Bio, Wugen, Allovir, Adicet, BMS, Molecular Template, Atara and Merck. He also received consulting fees from MJH BioScience, Arivan Research, Janssen, ADC Therapeutics, Gilead, GSK, Caribou, Roche, Autolus, Poseida, AstraZeneca, travel support from Poseida, and has fiduciary role at NCCN and ASH. SP received support for speakers bureau participation from Kite Pharma and Sanofi, and is on the advisory board for CareDx. YC received consulting fees from Incyte, CSL Behring, MaaT Biotherapeutics, Ironwood, LifeMine, ProTGen, and Generation Bio, is on the trial committee for Novo Nordisk, Editas, Alexion and Daiichi, and received equity in ImmunoFree and Phesi. JP received compensation from Orca Bio for participation in advisory board post conclusion of the Precision-T Phase 3 trial. RN received consulting fees from Amgen, Garuda now StratusTherapeutics, Biorasi, Apia Bio, Cellenko, and ReStem. He was the inventor of an allogeneic transplantation patent that has been licensed to Orca Bio, served on the advisory/data safety monitoring board of Kura Oncology and University of Pennsylvania, is the Vice President and President Elect of American Society of Hematology, and received stock options from Garuda Therapeutics (now Stratus Therapeutics). BH received research funding from Incyte, payment from CSL Behring for educational video and from PeerView for attending and presenting at educational symposia. In addition, she is on the advisory board of Sanofi and Maat Pharma, on the adjudication committee of CSL Behring and on the DSMB committee of Angiocrine. JHC received a GVHD adjudication grant, support for attending American Society of Hematology (ASH) as executive board member and held leadership position at ASH, ASTCT, Access Initiative of ASTCT and NMDP and CIBMTR. SK (University of Chicago) received one-time payment from

Sanofi and AbbVie for chronic GVHD and MDS lectures, respectively, and travel support from Sanofi for advisory board meeting. He is on the advisory board of Incyte and Sanofi, serves on the data and safety monitoring board of Cartesian Therapeutics, and is a member of BMT-CTN. RT, RH, AE, EKW have no interests to declare related to this study.

Data sharing

Orca Bio ensures that authors have appropriate access to essential study documentation, including study reports, final protocols, statistical analysis plans, statistical tables and figures. Orca Bio is committed to promoting public health by providing clinical trial data to external medical specialists and scientific researchers. Orca will supply anonymized individual patient data (IPD) upon request or when required by applicable laws and regulations. Qualified external investigators may access IPD from studies of Orca Bio products 6 months after they have obtained regulatory approval in the United States and European Union. Orca Bio will review each request on a case-by-case basis, considering the scientific value of the proposed research, data accessibility, and planned usage. When Orca Bio authorizes data sharing for research activities, applicants must sign a data sharing agreement to ensure patient privacy protection before receiving any materials.

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Characteristic	Orca-T (N = 93)	Tac/MTX (N = 94)	All Patients (N = 187)
Male sex — no. (%)	53 (57.0)	50 (53.2)	103 (55.1)
Race or ethnic group — no. (%)†			
Hispanic or Latinx ethnic group			
Hispanic or Latinx	26 (28.0)	24 (25.5)	50 (26.7)
Not Hispanic or Latinx	62 (66.7)	59 (62.8)	121 (64.7)
Not reported or unknown	5 (5.4)	11 (11.7)	16 (8.6)
American Indian or Alaska Native	1 (1.1)	2 (2.1)	3 (1.6)
Asian	10 (10.8)	8 (8.5)	18 (9.6)
Black	1 (1.1)	2 (2.1)	3 (1.6)
Native Hawaiian or Pacific Islander	1 (1.1)	1 (1.1)	2 (1.1)
White	76 (81.7)	63 (67.0)	139 (74.3)
Not reported or unknown	4 (4.3)	18 (19.1)	22 (11.8)
Recipient Age			
Mean — yr	43.4±12.6	43.8±12.9	43.6±12.7
≥18 to <55 — no. (%)	70 (75.3)	67 (71.3)	137 (73.3)

≥55 to ≤65 — no. (%)	23 (24.7)	27 (28.7)	50 (26.7)
Karnofsky performance-status score ≥90 — no. (%)‡	71 (76.3)	65 (69.1)	136 (72.7)
Primary disease — no. (%)			
Acute lymphoblastic leukemia	30 (32.3)	27 (28.7)	57 (30.5)
Acute myeloid leukemia	49 (52.7)	51 (54.3)	100 (53.5)
Myelodysplastic syndrome	12 (12.9)	11 (11.7)	23 (12.3)
Mixed phenotype acute leukemia	2 (2.2)	5 (5.3)	7 (3.7)
Disease risk index category — no. (%)			
High risk	18 (19.4)	18 (19.1)	36 (19.3)
Intermediate risk	75 (80.6)	76 (80.9)	151 (80.7)
Donor type — no. (%)			
Matched sibling donor	46 (49.5)	49 (52.1)	95 (50.8)
Donor age			
Mean — yr	37.5±13.1	35.2±12.4	36.4±12.7
≥18 to <55 — no. (%)	79 (84.9)	85 (90.4)	164 (87.7)
≥55 to ≤65 — no. (%)	14 (15.1)	9 (9.6)	23 (12.3)

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. * The intention-to-treat population consisted of all patients who underwent randomization. The experimental-treatment arm received Orca-T plus tacrolimus, and the standard-treatment arm received G-CSF-mobilized peripheral blood plus tacrolimus–methotrexate. †Race or ethnic group was reported by the investigators. ‡ Karnofsky performance-status scores range from 0 to 100, in 10-point increments, with higher scores representing better well-being and performance status.

Outcome	**Treatment Arm**	
	Orca-T (N=88)	**Tac/MTX (N=94)**
Neutrophil engraftment by day 28 [95% CI (L, U)]*	100 (100, 100)	96.7 (89.5, 99.0)
Days to neutrophil engraftment [Median (Q1,Q3)]†	13.0 (12.0, 15.0)	14.0 (12.0, 16.0)
Platelet engraftment by day 50	98.9 (86.8, 99.9)	92.5 (84.4, 96.4)
Days to platelet engraftment [Median (Q1,Q3)]	17.0 (15.0, 18.0)	18.0 (15.0, 20.0)
Grade 2-4 acute GVHD (MAGIC) at 6 months	20.1 (12.3, 29.4)	27.4 (18.4, 37.2)
Grade 3-4 acute GVHD (MAGIC) at 6 months	6.2 (2.3, 12.9)	16.5 (9.4, 25.3)
Estimated Cumulative Incidence at 1-yr [95% CI (L, U)]		
Overall survival (OS)	93.7 (85.4, 97.4)	83.2 (73.0, 89.8)
Relapse-free survival (RFS)	75.5 (63.0, 84.3)	74.1 (62.7, 82.5)

Non-relapse mortality (NRM)	3.4 (0.9, 8.8)	13.2 (6.8, 21.6)
All grade chronic GVHD	21.9 (11.7, 34.2)	67.5 (53.9, 77.9)
Moderate or severe chronic GVHD	12.6 (5.3, 23.1)	44.1 (31.3, 56.1)
Infections Grade 2 or 3	46.9 (35.7, 57.3)	44.1 (33.0, 54.7)
Infections Grade 3	8.4 (3.6, 15.7)	16.1 (9.2, 24.7)
Incidence of Safety Events (% of participants)		
Serious treatment-emergent adverse events (TEAE)	34 (38.6)	53 (56.4)
Number of participants re-hospitalized due to AE	24 (27.3)	43 (45.7)
Number of participants admitted to ICU	1 (1.1)	4 (4.3)
Total days hospitalized (% of total days alive)		
Day+0 – day+21	1467 (79.4)	1604 (81.3)
Day+22 – day+100	224 (3.4)	647 (9.4)
Day+101 – 2 years	211 1.0)	701 (3.4)

Table 2. Major Treatment Outcomes.

Safety population data shown. CI, confidence interval; Q1, first quartile; Q3, third quartile; GVHD, graft-versus-host disease; MAGIC, Mount Sinai Acute GVHD International Consortium.
* 95% confidence parameters fall between lower and upper values. †Median of first and third quartile. Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) ≥500/mm^3 for 3 consecutive days by day +28. The first of the 3 days was designated the day of engraftment. Platelet engraftment is defined as achieving a platelet count >20,000/mm^3 for 3 consecutive days by day +50 without platelet transfusion in the preceding 7 days. The first of the 3 days was designated the day of engraftment.

Infections grading per BMT CTN MOPS criteria.

Figure 1. CONSORT diagram detailing Randomization, Treatment, and Follow-up.

a) Treatment was delayed due to SARS-CoV-2 infection. The patient subsequently received unmanipulated PBSC with Tac/MTX.
b) Due to matched donor becoming unavailable.
c) As treated population.
d) As treated population. Includes the patient randomized to the Orca-T arm who received Tac/MTX and excludes the Haplo/PTCy patient.

Figure 2. Survival Probabilities and the Cumulative Incidence of Primary and Secondary End-Point Events. (A) The survival free from moderate-to-severe chronic GVHD (the primary endpoint) following Orca-T or Tac/MTX prophylaxis over 1 year. Shaded areas indicate 95% simultaneous confidence bands. (B) The cumulative incidence of moderate-to-severe chronic GVHD (cGVHD) over one year. (C) The OS probability over one year. (D) The survival free from acute GVHD grades III-IV, moderate-to-severe chronic GVHD, or relapse (GRFS) over one year. For the estimates of the secondary end-point events, 95% confidence intervals for survival and cumulative incidence at one year (Panels B through D) are provided, but they have not been adjusted for multiplicity and should not be used for hypothesis testing.

Figure 3. Immunological associations with infection and treatment-related mortality. (A) CD4+ T cell counts measured in fresh whole blood at scheduled visits post-transplant. Solid circles denote median values, while shading indicates the 25^{th}-75^{th} percentiles. (B) Treg frequencies shown in fresh whole blood collected 14 days post-transplant from participants in the Orca-T and Tac/MTX arms. Treg frequencies are defined here as the percentage of $CD25^{bright}$ $CD127^{dim}$ cells among total $CD3^{+}$ $CD4^{+}$ lymphocytes. Boxes reveal the 25^{th}, 50^{th}, and 75^{th} percentiles, while whiskers denote the 10^{th} and 90^{th} percentiles. Median values are provided within the boxes. P value was derived from Rank Sum test. (C) Cumulative incidence of grade 3 infections in each treatment arm is depicted. Infections were graded based on the BMT CTN MOP scoring. (D) Primary causes of death are shown for each treatment arm. Causes of NRM are indicated by the hatched fills.

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Figure 1

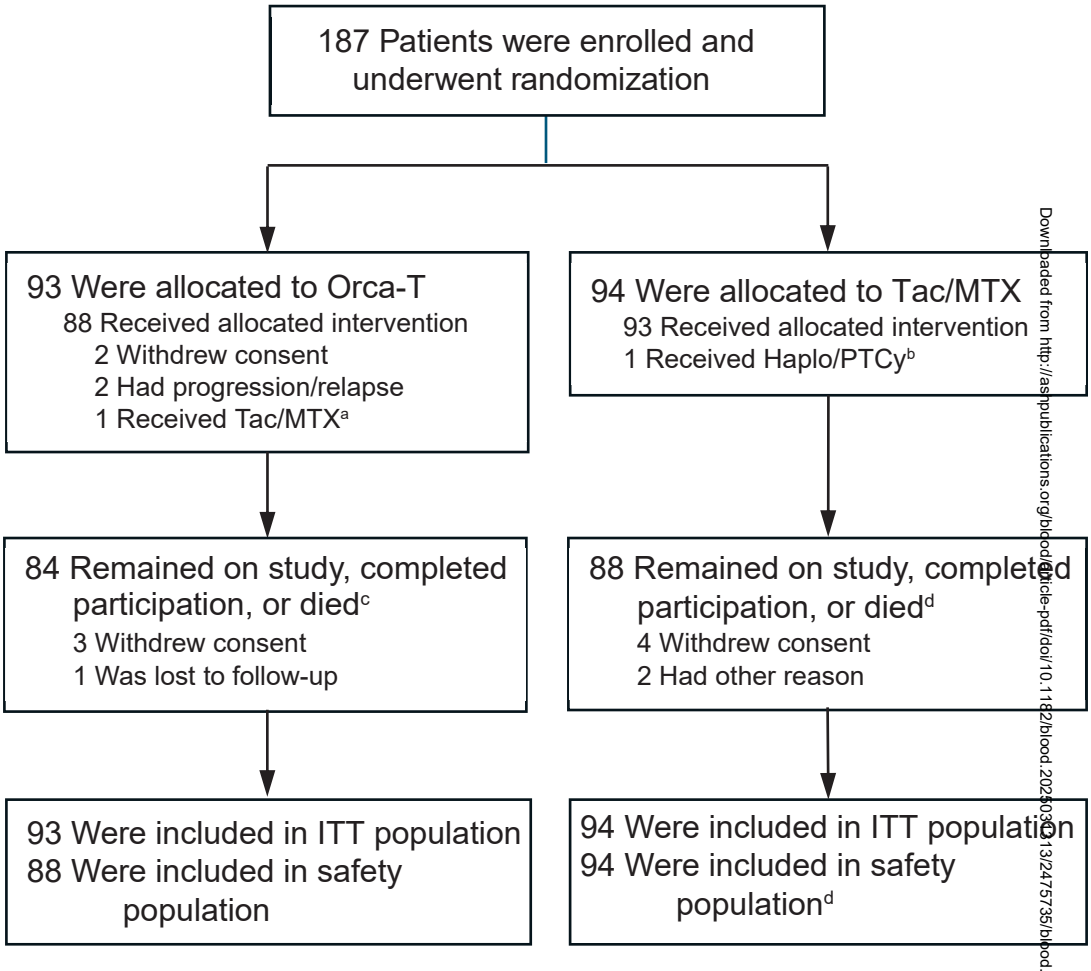


Figure 2

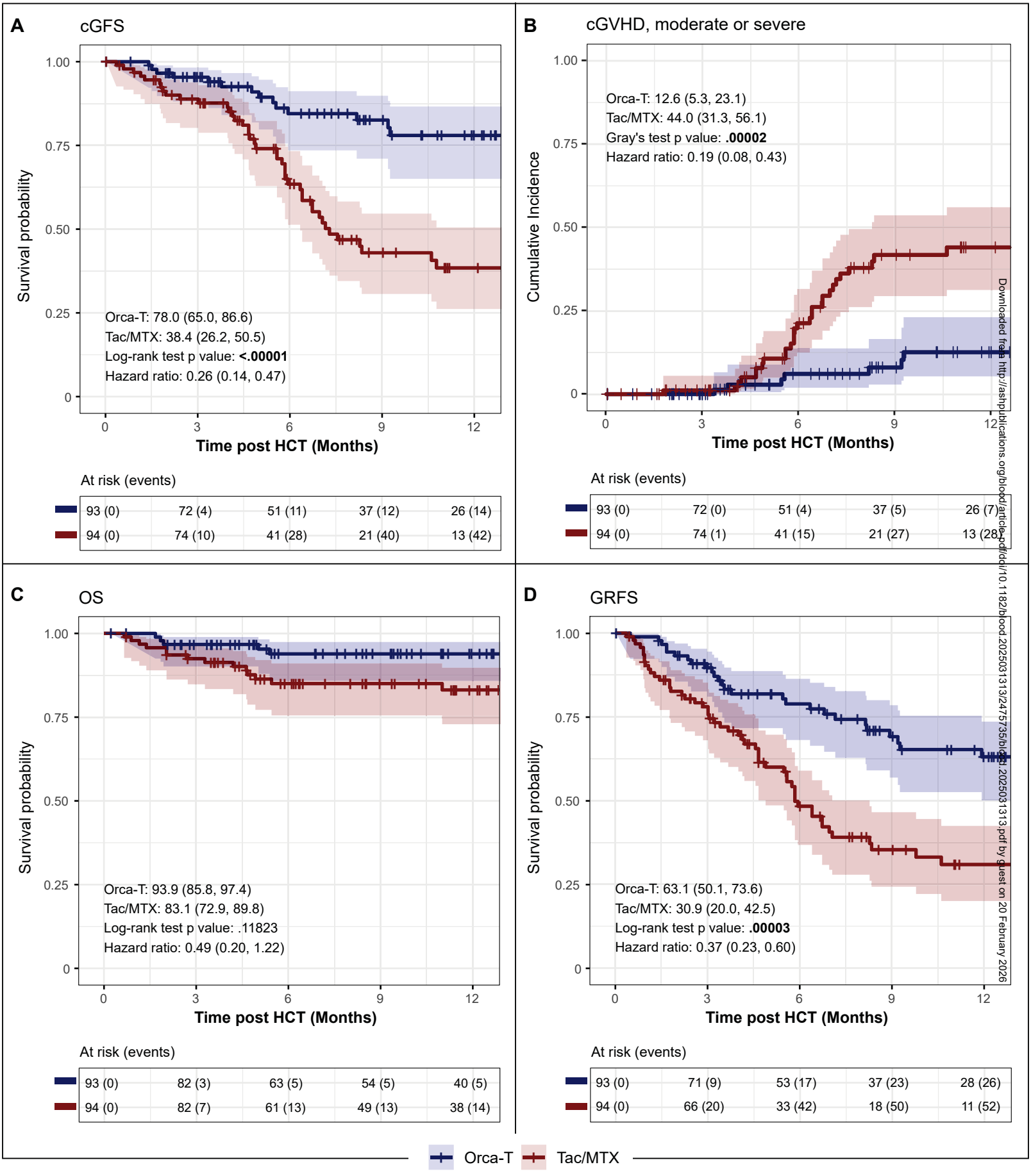
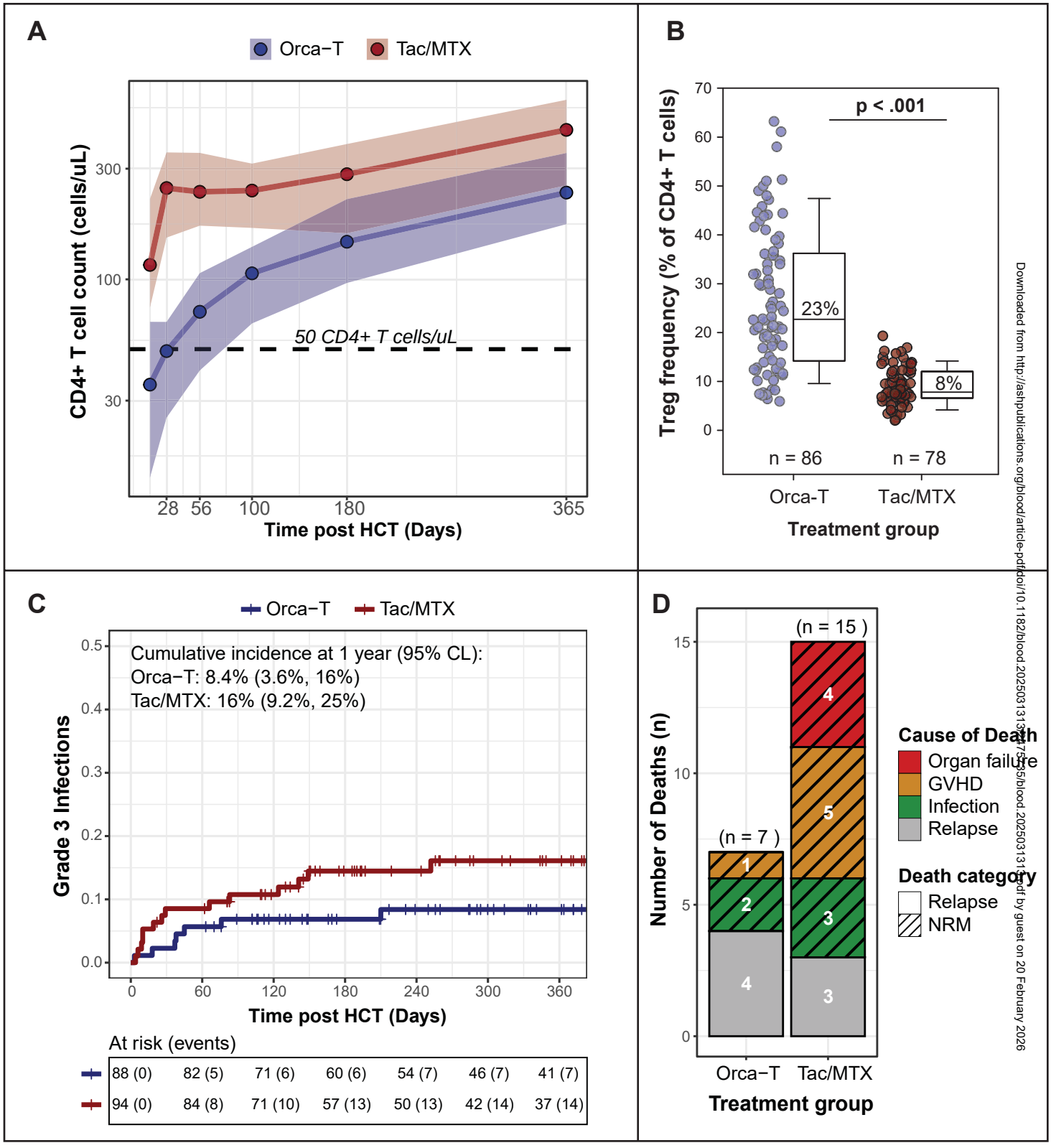


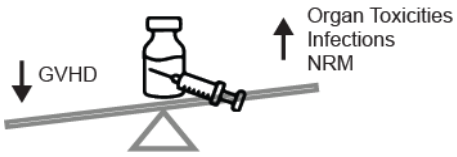
Figure 3



Precision-T: A Randomized Study of Orca-T in Recipients Undergoing Allogeneic Transplantation for Hematologic Malignancies

Context of Research

- Following allogeneic HSCT, pharmacological immune suppression reduces GVHD but risks other complications. Novel strategies are needed.



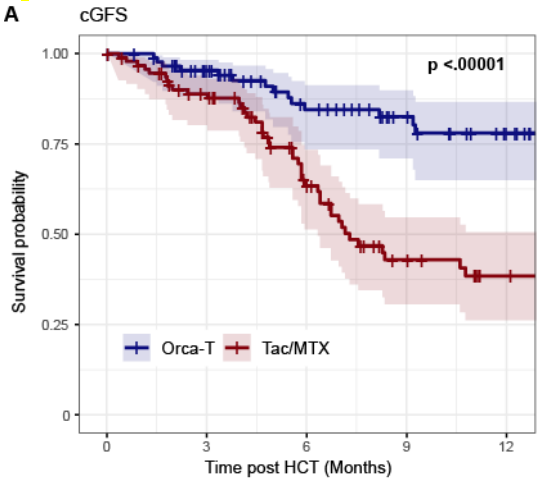
- **Orca-T** is a cell therapy that uses high-purity regulatory T cells to prevent GVHD.

Patients and Methods

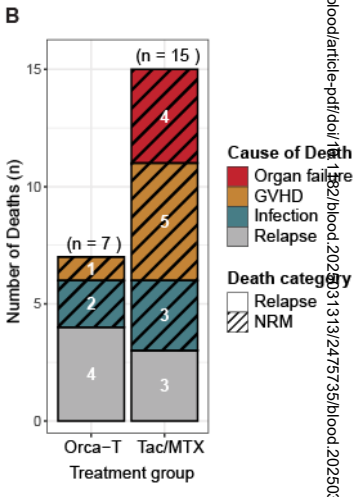
- **ClinicalTrials.gov ID NCT05316701**
- Adult patients with AML, ALL, MPAL, or MDS
- Randomized to Orca-T with single-agent tacrolimus (n=93) or a conventional allograft with tacrolimus and methotrexate (n=94)
- Primary endpoint: survival free from moderate-to-severe chronic GVHD (cGFS)

Main Findings

A) Orca-T improved survival free from moderate-to-severe chronic GVHD (primary endpoint)



B) There were fewer deaths with Orca-T, which was due to less non-relapse mortality



Conclusions: Despite less pharmacological GVHD prophylaxis, Orca-T improved survival free from chronic GVHD due to less GVHD and fewer deaths. Orca-T patients also had fewer serious infectious complications, fewer re-hospitalizations, and less non-relapse mortality.

*Meyer et al. DOI: 10.xxxx/**blood**.2025xxxxxx*

blood Visual Abstract