CT-524

Orca-T Results in High GVHD-Free and Relapse-Free Survival Following Myeloablative Conditioning for Hematological Malignancies

Anna Pavlova, Rasmus Hoeg, Arpita Gandhi, Lori Muffly, Parveen Shiraz, Caspian Oliai, Rohtesh S. Mehta, Samer A. Srour, Joseph McGuirk, Edmund K. Waller, Amandeep Salhotra, Sally Arai, Laura Johnston, Robert Lowsky, Andrew Rezvani, Wen-Kai Weng, David Miklos, Matthew Frank, Vaibhav Agrawal, Nathaniel B. Fernhoff, Gerhard Bauer, Amy Putnam, J. Scott McClellan, M. Scott Killian, Bronwen E. Shaw, Mehrdad Abedi, Robert S. Negrin, Everett H. Meyer

BACKGROUND

- Graft versus host disease (GVHD) remains a leading cause of morbidity and mortality following allogeneic hematopoietic stem cell transplant (alloHSCT). Strategies to reduce GVHD have been limited in efficacy or compromised by increased risk of infection and relapse. There is an urgent need for alternative strategies that holistically improve outcomes.
- Orca-T is a high-precision, allogeneic investigational cell therapy product comprised of stem and immune cells that leverages highly purified, polyclonal donor regulatory T cells to control alloreactive immune responses. Orca-T is produced in a central GMP facility and has been successfully scaled to clinical centers throughout the U.S. Orca-T shows a favorable safety profile and promising control of both GVHD and relapse.

METHODS

Through 1 March 2022, 137 patients with high-risk hematologic malignancies received Orca-T in a single-center Phase 2 study (NCT01660607, n=34) and multicenter Phase 1b study (NCT04013685, n=103) and have ≥ 100 days of follow-up (or died prior to Day +100; range 27-1988 days). Patients underwent transplant between from July 2016 and December 2021. Median follow-up for patients is 341 days. Patients received investigator's choice of myeloablative conditioning regimens (busulfan-based, n=99; TBI-based, n=38) followed by single-agent prophylaxis with either tacrolimus (n=130) or sirolimus (n=7). For comparison purposes, an independent CIBMTR-based control arm was identified which consisted of patients with hematologic malignancies who received myeloablative alloHSCT with a PBSC source over a similar timeframe (2016-2018) followed by tacrolimus plus methotrexate GVHD prophylaxis (n=375, 69 transplant centers across the United States). A Phase 3 study comparing Orca-T to a standard-of-care, unmanipulated allograft has been initiated.

Patient demographics are shown in Table 1:

Table 1

	Orca-T (Multicenter Phase 1b)	Orca-T (Single-Center Phase 1/2)	CIBMTR Control Cohort
Cohort size	**103**	**34**	**375**
Median age (range)	51 (19-65)	42 (19-71)	52 (18-65)
% Male	52%	71%	57%
Race — White	74%	60%	73%
African American	1%	0%	9%
Asian	11%	20%	12%
Unspecified/Unreported	14%	20%	6%
Primary Disease % — AML	43%	41%	47%
ALL	32%	17%	20%
MDS	13%	2%	33%
myelofibrosis	7%	7%	0%
CML	3%	12%	0%
Non-Hodgkin Lymphoma	0%	10%	0%
Other (e.g. mixed phenotype acute leukemia)	2%	11%	0%
Myeloblative regimen: Busulfan-based/TBI-based	78% / 22%	76% / 24%	77% / 20%
Graft source: HLA-matched siblings/ HLA-matched unrelated donor	54% / 46%	74% / 26%	45% / 55%
Median f/u in days (range)	313 days (27 – 859)	367 days (104 – 1988)	900 days (120-1500)

RESULTS

Figure 1. ***Neutrophil and platelet engraftment has been rapid following Orca-T plus single-agent GVHD prophylaxis.*** Neutrophil and platelet engraftment occurred at median of 13 and 15 days, respectively. Two graft failure events (1.4%) have been reported out of 137 patients treated with Orca-T.

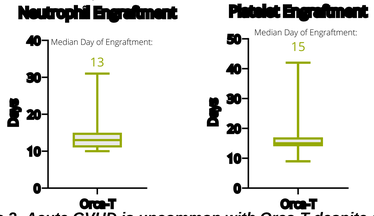


Figure 2. ***Acute GVHD is uncommon with Orca-T despite a limited GVHD prophylaxis regimen.*** The rates of Grade ≥ 2 and Grade ≥ 3 aGVHD were 17% and 4% (graded per MAGIC criteria), respectively, through Day +180 with Orca-T plus single-agent GVHD prophylaxis. Only 4 patients (3%) experienced steroid-refractory or steroid-dependent aGVHD.

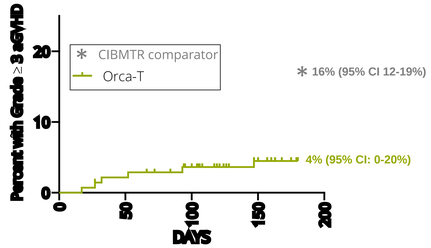


Figure 3. ***Moderate/severe chronic GVHD is rare with Orca-T.*** The rate of NIH moderate to severe cGVHD was 5% through 1 year post-transplant.

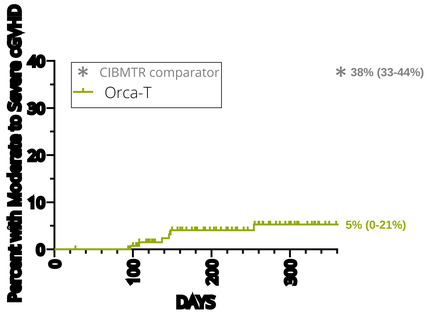


Figure 4. ***Despite reduced GVHD rates, relapse rates following Orca-T are not elevated compared to historic controls, suggesting that graft-vs-leukemia effects remain intact with Orca-T.*** Of note, patients with active leukemia at time of transplant were allowed to enroll on Orca-T studies provided that bone marrow blast burden was ≤ 10%. 14% of patients enrolled had active leukemia at transplant; similarly, 16% of the comparator cohort had "advanced" disease.

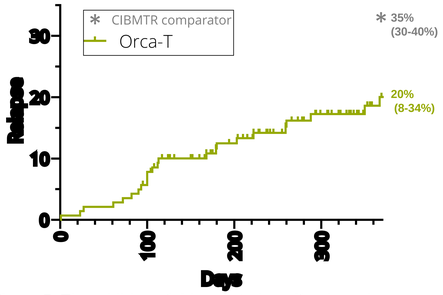


Figure 5. ***The addition of thiotepa to busulfan-based conditioning regimens decreases relapse without increasing non-relapse mortality with Orca-T.*** Relapse-free survival through 1 year is shown for all Orca-T patients (n=137), Bu/Flu or Bu/Cy conditioning prior to Orca-T (n=50), and Bu/Flu/Thiotepa conditioning prior to Orca-T (n=49)

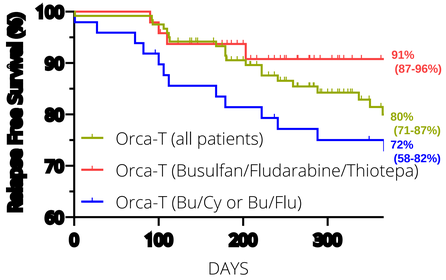


Figure 6. ***Lymphocyte subset reconstitution.*** Shown are the absolute cell counts per microliter of whole blood of T cells, CD4+ T cells, CD8+ T cells, regulatory T cells, B cells, and NK cells in recipients pre-transplant and during the first year post-transplant. The number of patients included at each time point is indicated in each graph. Blue circles and bars show the median and quartile values.

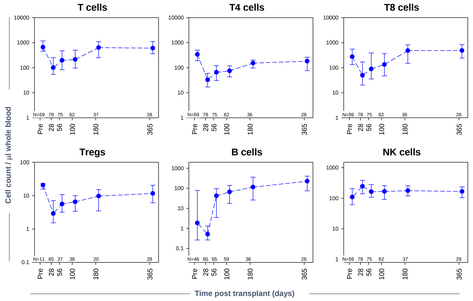


Figure 7. ***Severe infection is uncommon in patients treated with Orca-T.*** Shown is the incidence of Grade 3 infections using the BMT-CTN MOP V4.0 grading scale. COVID-19/SARS-COV2 infections were reported in 13 patients and resulted in one death.

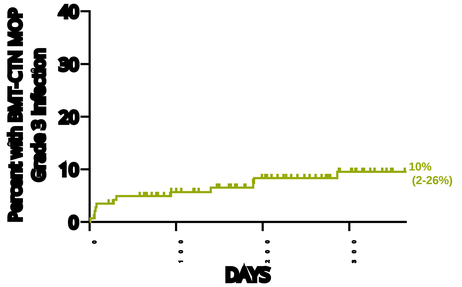


Figure 8. ***Orca-T plus single-agent GVHD prophylaxis results in GVHD and relapse-free survival (GRFS) at 1 year that is superior to historic comparators.*** Modified GRFS is shown: survival free of Grade 3-4 aGVHD, moderate to severe cGVHD, and relapse.

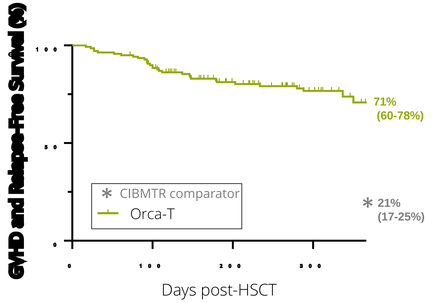
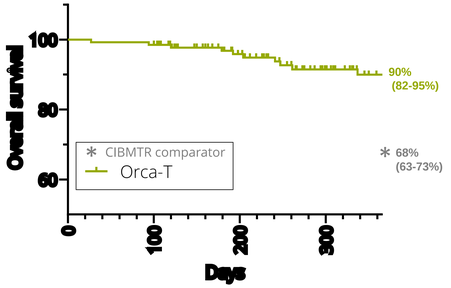


Figure 9. ***Preliminary overall survival data suggests that Orca-T may lead to improved survival in patients undergoing allogenic hematopoietic stem cell transplant (alloHSCT) for high-risk hematologic malignancies.***



CONCLUSIONS

- Orca-T is a high-precision, allogeneic investigational cell therapy that replaces conventional alloHSCT. To date, an Orca-T product has been successfully produced for more than 160 patients.
- Compared to historic controls, Orca-T plus single-agent GVHD prophylaxis has led to reduced aGVHD and cGVHD without a concomitant increase in relapse or severe infection. Preliminary data suggests that immune reconstitution after Orca-T is robust.
- Experience with Orca-T in two Phase 1/2 trials suggests that this approach may yield significant improvements in GRFS and overall survival.
- Orca-T is being evaluated in a randomized Phase 3 study (Precision-T) which is now enrolling at transplant centers across the United States.