Orca-T Results in High GVHD-Free and Relapse-Free Survival Following Myeloablative Conditioning for Hematological Malignancies: Results of a Single Center Phase 2 and a Multicenter Phase 1b Study

Data presented at the European Hematology Association 2022 Congress

Opportunity to improve clinical outcomes from allogeneic HSCT by optimizing allograft

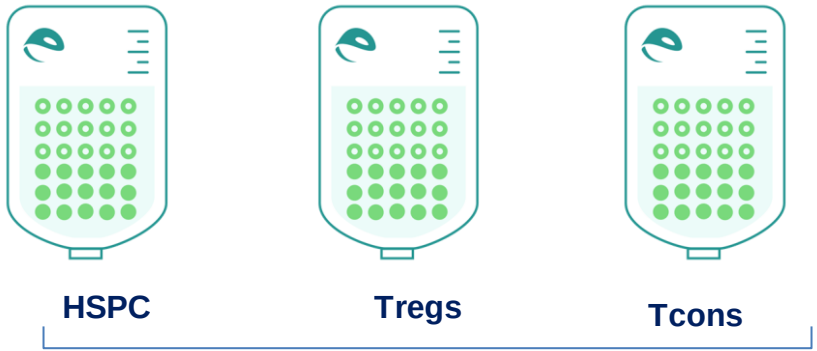
Current Transplants

Uncontrolled mix of over 50 cell types

Hematopoietic stem cells
Progenitor cells
Conventional T cells
T regulatory cells
NK cells
Invariant NKT cells
Dendritic cells
Myeloid derived suppressor cells

Orca's Precision Engineered Allografts

Defined Cell Population



1:1 ratio Treg:Tcon

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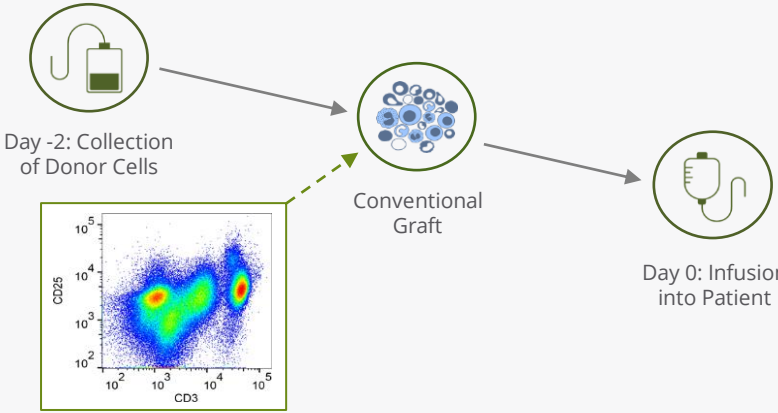
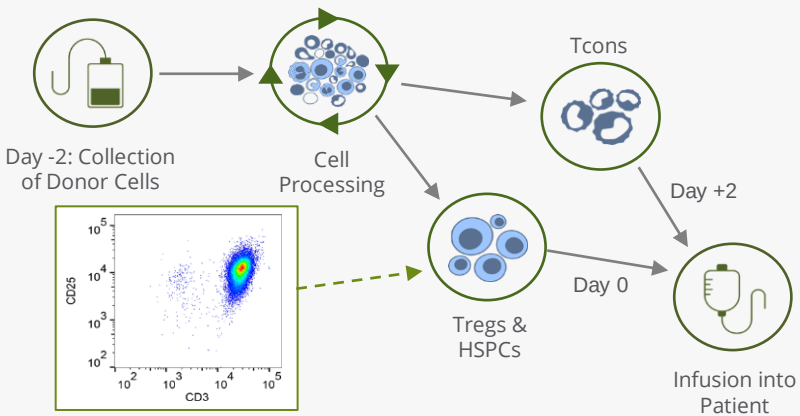
Orca-T is a precision cell therapy product designed to fit into traditional transplant center protocols

Conventional Transplant



High-Precision Orca-T



Eddinger et al. Nature Medicine 2003 Sep;9(9):1144-50. | Trzonkowski et al. Clin Immunol. 2009 Oct;133(1):22-6. Di Ianni M, et al. Blood. 2011;117(14):3921–3928. | Brunstein, et al. Blood 2016 Feb 127 (8):1044-51. | Kellner H, et al. Oncotarget 2018 Nov 2;9(86):35611-35622.

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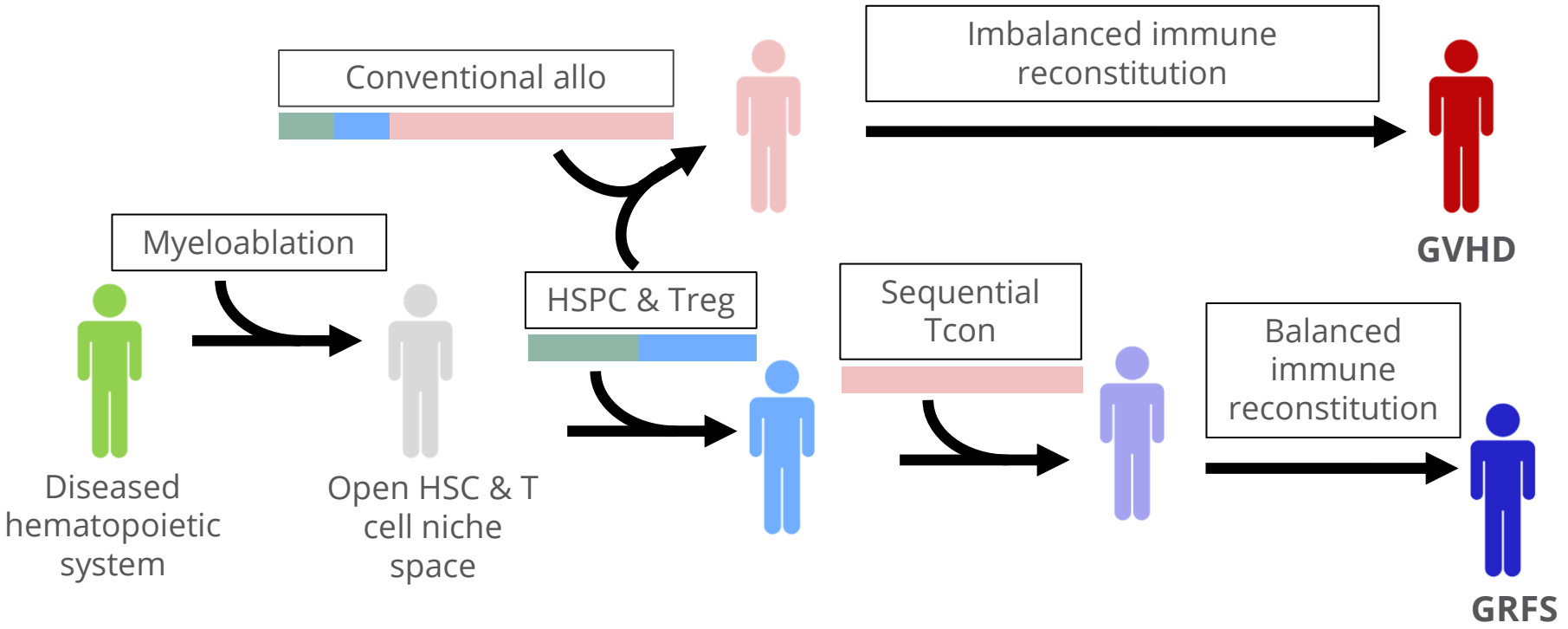
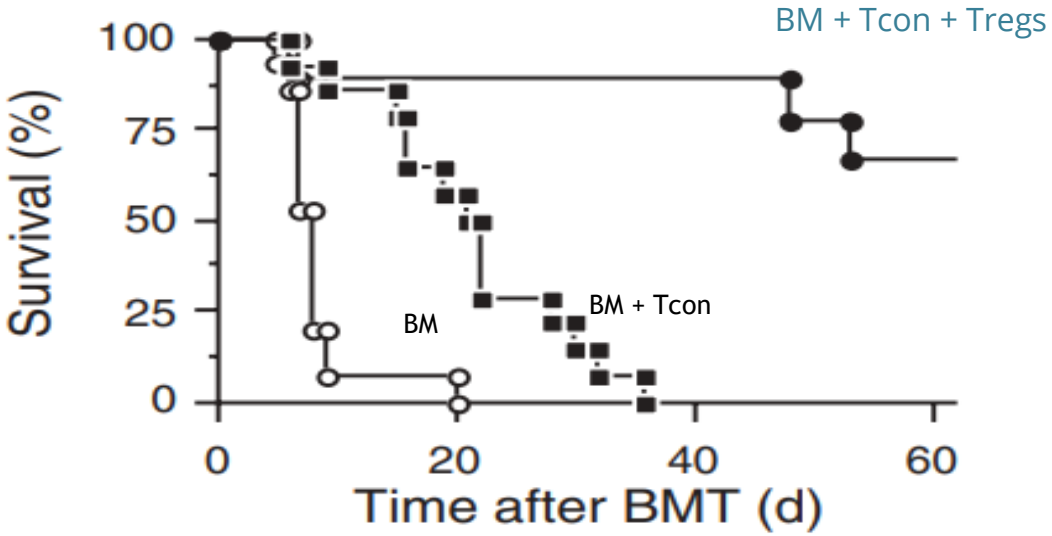
Orca-T leads to balanced immune reconstitution

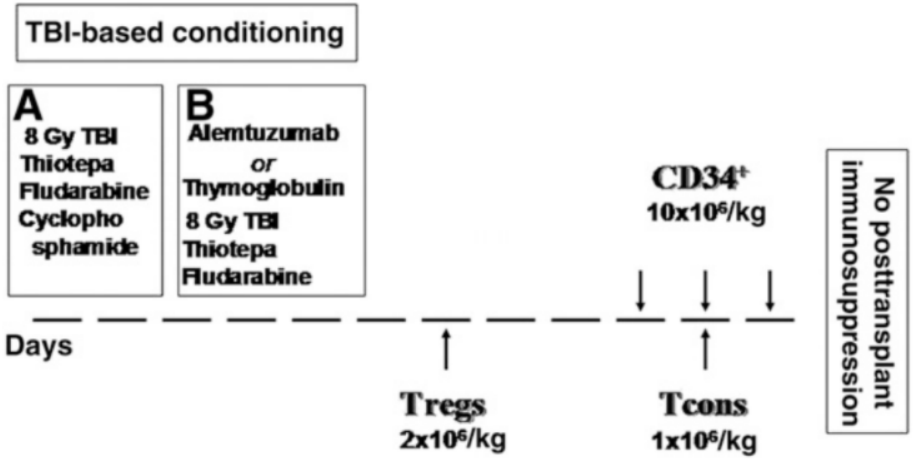


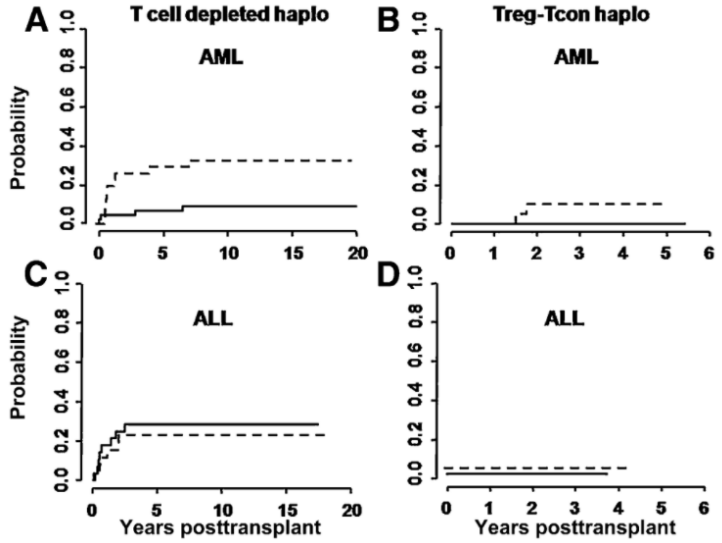
Treg transfer was demonstrated in preclinical mode: Enriching allografts with Tregs could improve HCT outcomes



Edinger *et al*, 2003

Treg transfer was demonstrated in early clinical trials: Enriching with Tregs could improve haplo HCT outcomes





Acute GVHD grade ≥2 rate 15%

Lower CI of relapse compared to TCD haplo (0.05 vs 0.21; P = .03)

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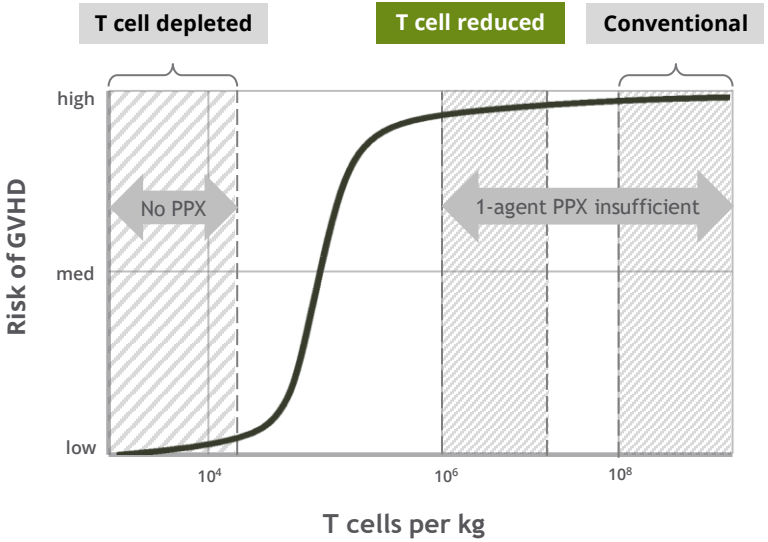
Martelli *et al*, 2014

Traditional T cell reduced grafts require 2 agent GVH prophylaxis for T cell doses ≥ 1 x 10^6 cells/kg

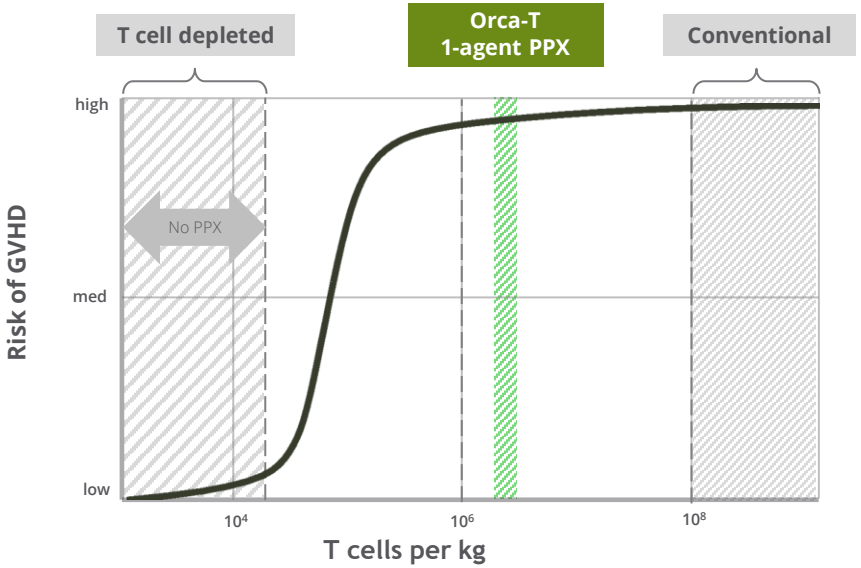


T cell reduced grafts

- Previous studies employing T cell reduction of allografts alone still show significant acute and chronic GVHD with single-agent cyclosporin prophylaxis*

*Montero et al. BBMT 12:1318-1325 (2006)
Nakamura et al. BJH 115:95-104 (2001)
Barrett et al. BMT 21: 543-551 (1998)

Orca-T graft requires only single agent GVH prophylaxis despite T cell doses 3 x 10^6 cells/kg



Orca-T + 1-agent PPX

- Yield of Treg from apheresis: 2-3 million Treg/kg
- Target ratio of T cell to Treg: 1:1
- Conventional T cell dose: 3 million/kg
- CD34 dose: >2 million/kg

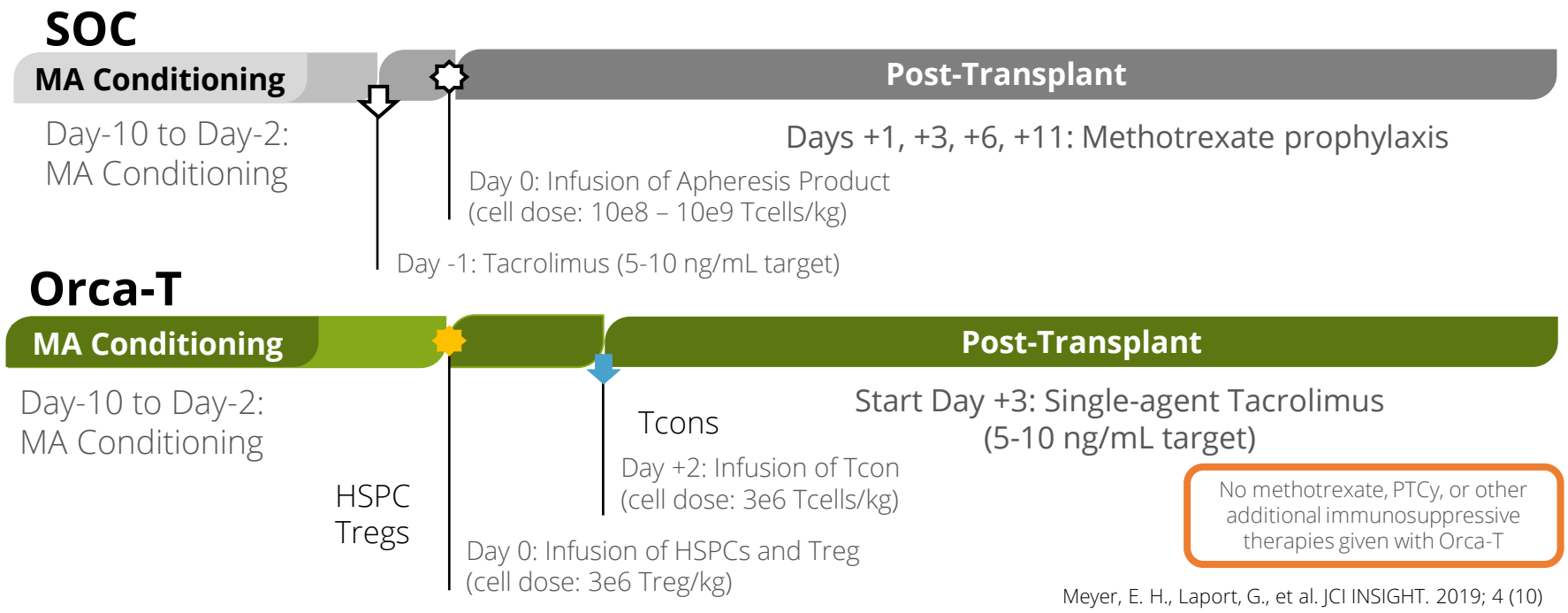
1:1 ratio Treg:Tcon

Montero et al. BBMT 12:1318-1325 (2006)
Nakamura et al. BJH 115:95-104 (2001)
Barrett et al. BMT 21: 543-551 (1998)

Key eligibility criteria for Orca-T single-institution phase 1/2 study and multicenter phase 1b study

Stanford Single Center Phase 2 Trial (NCT01660607)* Orca Multicenter Phase 1b Trial (NCT04013685)	
• Acute leukemia (AML, ALL, mixed phenotype), including patients with active disease at time of transplant (≤ 10% BM blast burden) • Myelodysplastic syndrome • Myelofibrosis • BPDCN • CML in accelerated phase or blast crisis • Non-Hodgkin Lymphoma*	
8/8 matched related or unrelated donor	
HCT-CI ≤ 4	
KPS ≥ 70	
Age 18-65 (or 18 – 72)*	
Adequate organ function	
Primary objective: Safety	Secondary objectives: OS, GRFS, aGvHD, cGvHD, serious infection, engraftment
Primary endpoints: Incidence and severity of Grade 3-4 aGVHD; incidence and timing of primary graft failure	

Orca-T treatment consisted of MAC with single-agent post-treatment tacrolimus & no methotrexate or PTCy



Meyer, E. H., Laport, G., et al. JCI INSIGHT. 2019; 4 (10)

An approach pioneered by Rob Negrin, Everett Meyer and colleagues at Stanford University

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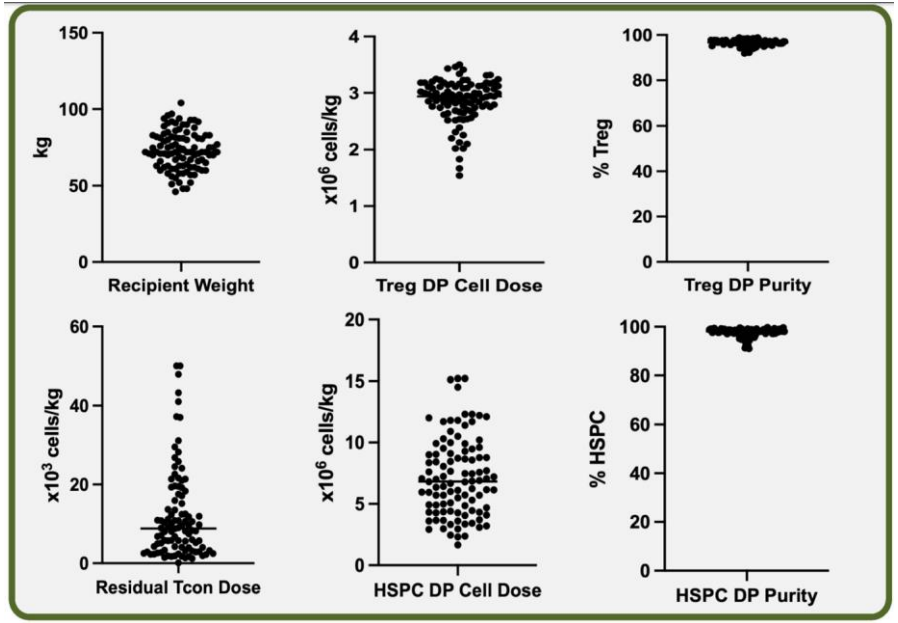
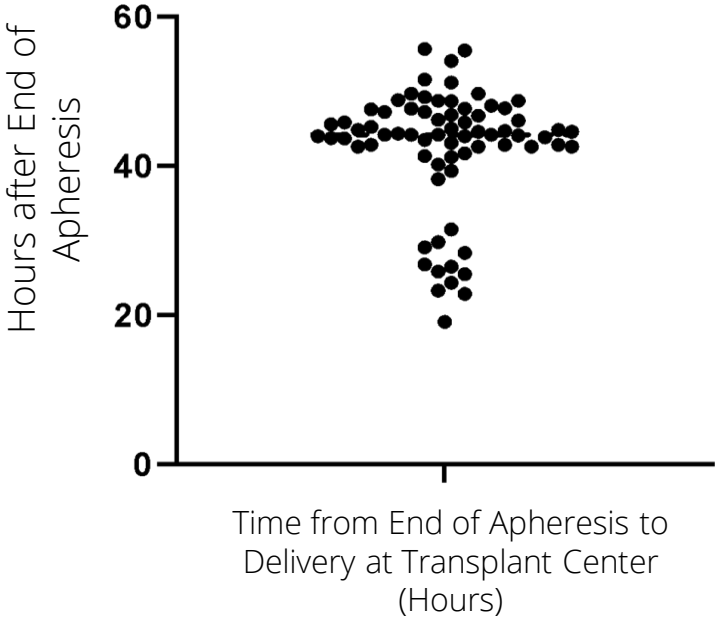
Orca manufacturing has reliably manufactured and delivered high-purity Orca-T at transplant centers across the US

High purity Orca-T products have been delivered to >130 patients to date



Vein-to-vein times of <72 hours consistently achieved



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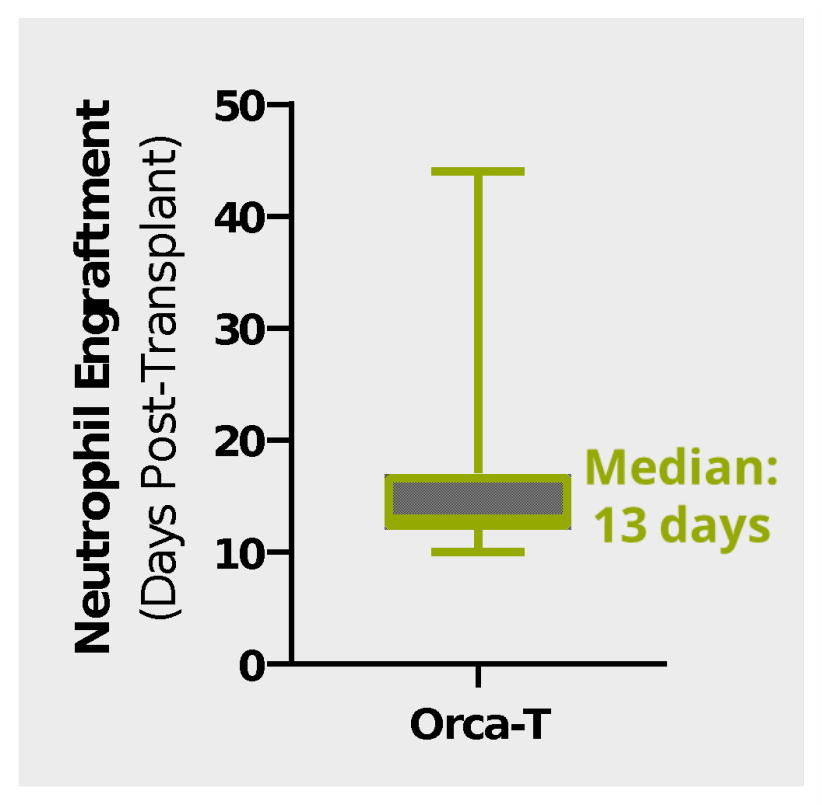
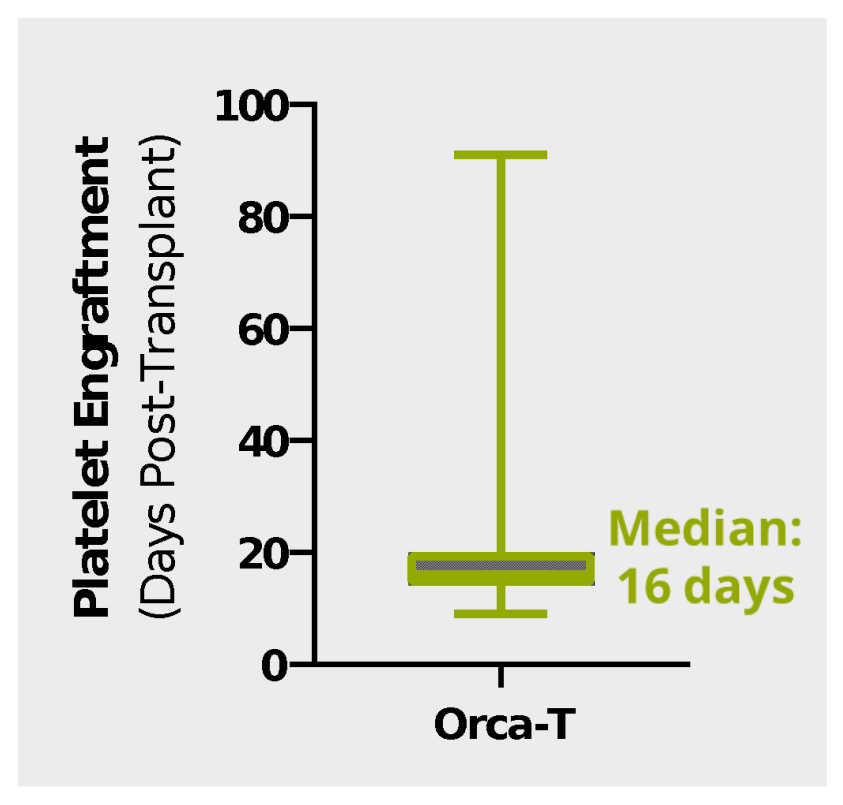
Orca-T in comparison to US multicenter historical cohort

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)

Rapid engraftment was observed with Orca-T

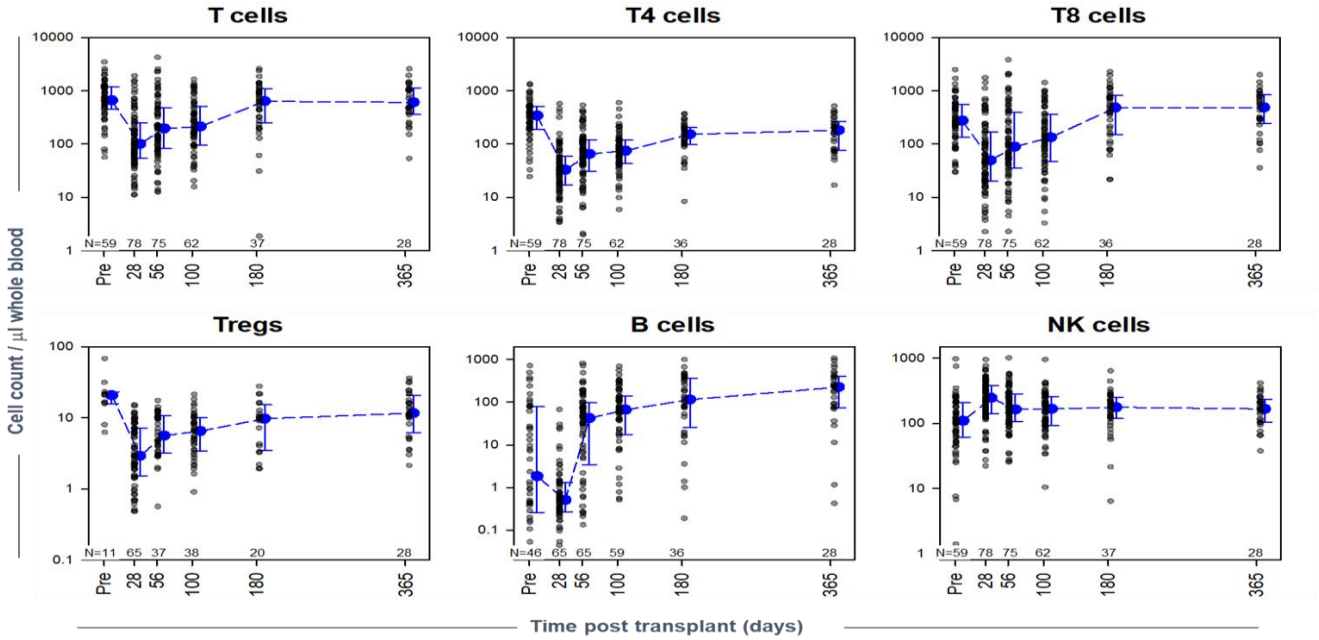




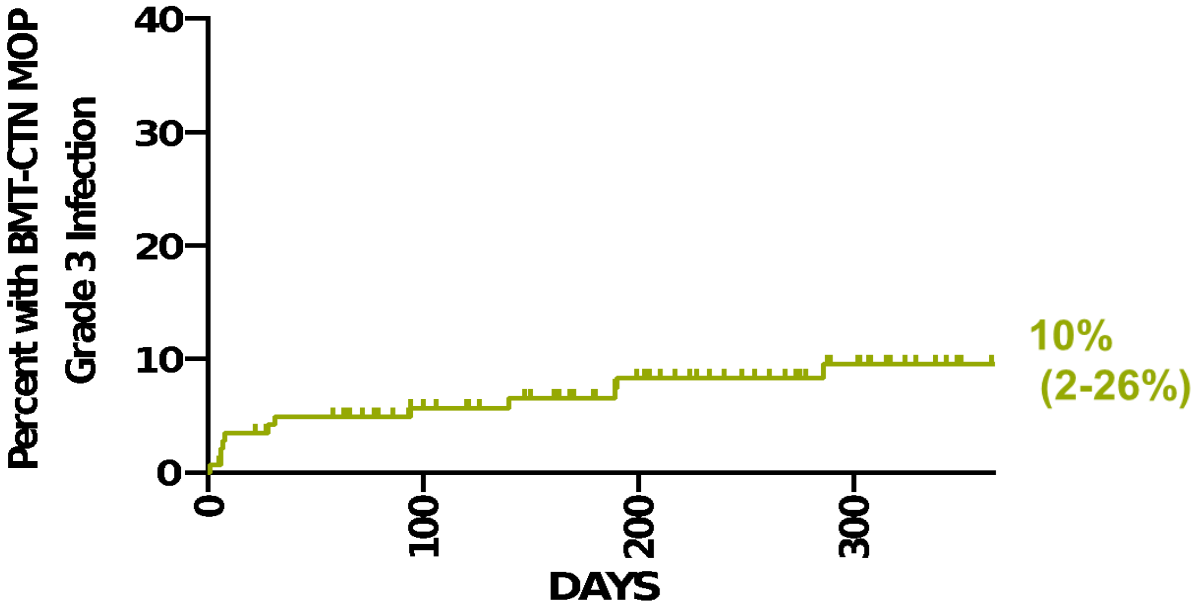
Orca-T achieves sufficient chimerism at standard timepoints

Leukocyte subset	Percentage of patients with ≥ 90% donor chimerism at Day +100
Granulocytes (CD33+)	100%
T cells (CD3+)	73%
B cells (CD19 or CD20+)	98%
NK cells (CD56+)	95%

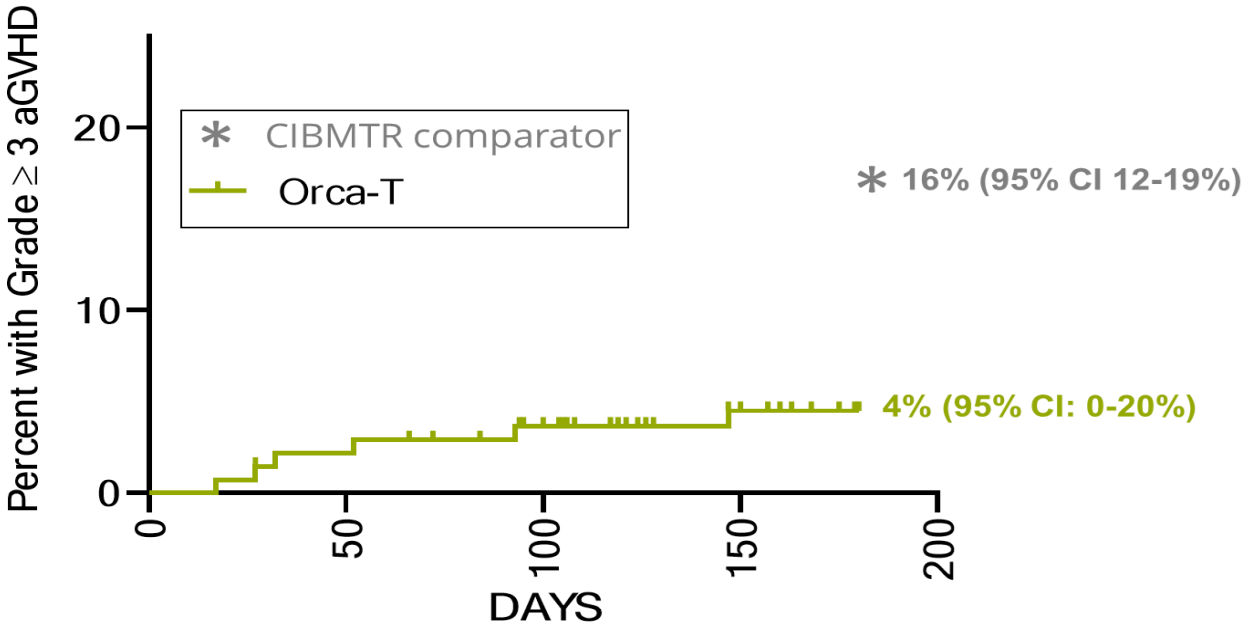
Immune reconstitution has been robust with Orca-T



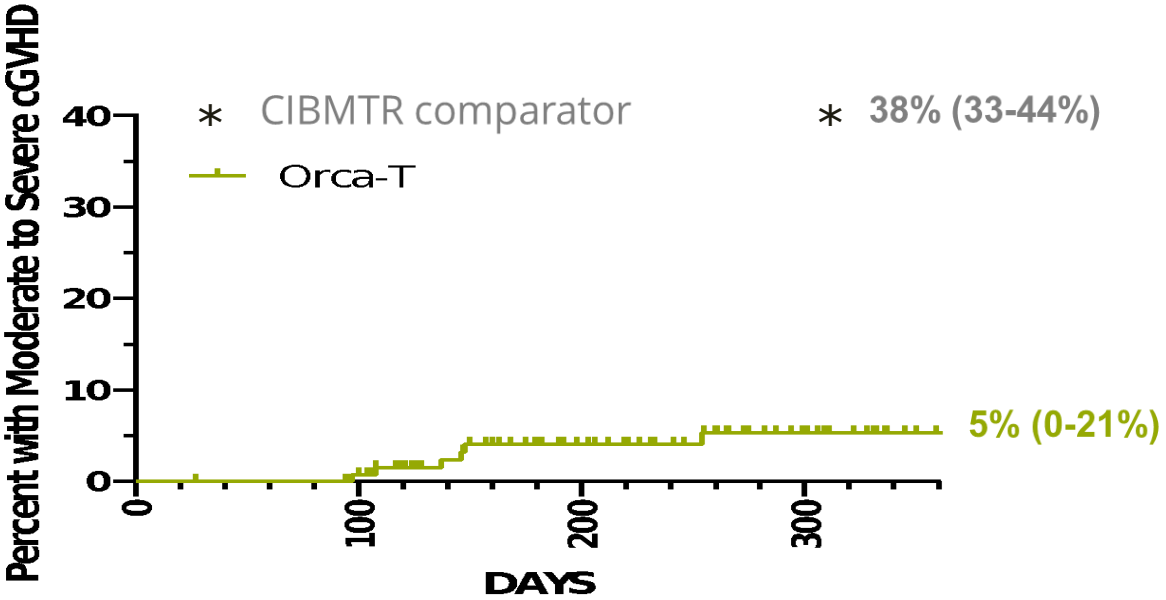
Severe infection was uncommon with Orca-T



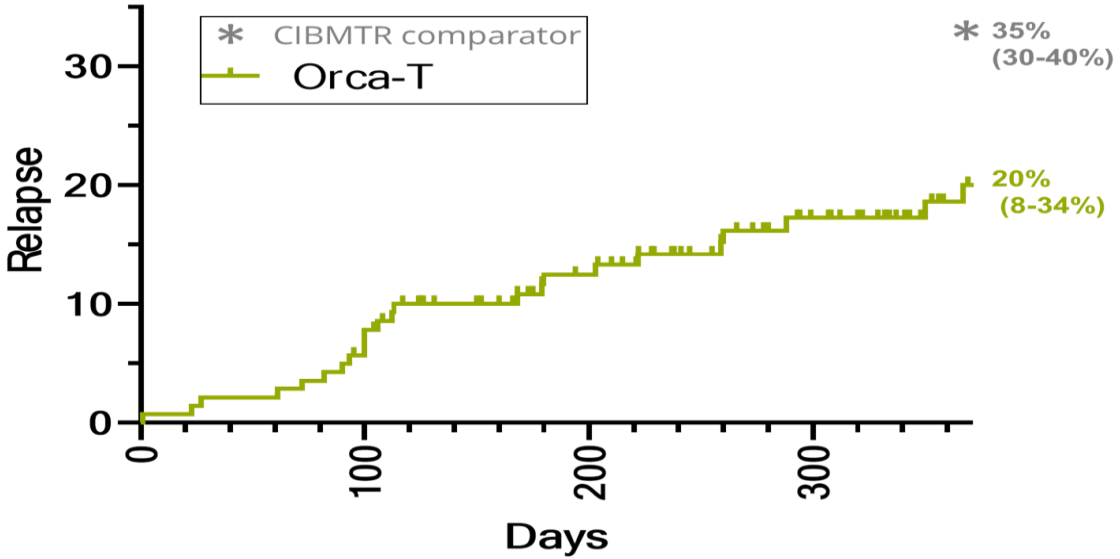
Severe acute GVHD was low with Orca-T



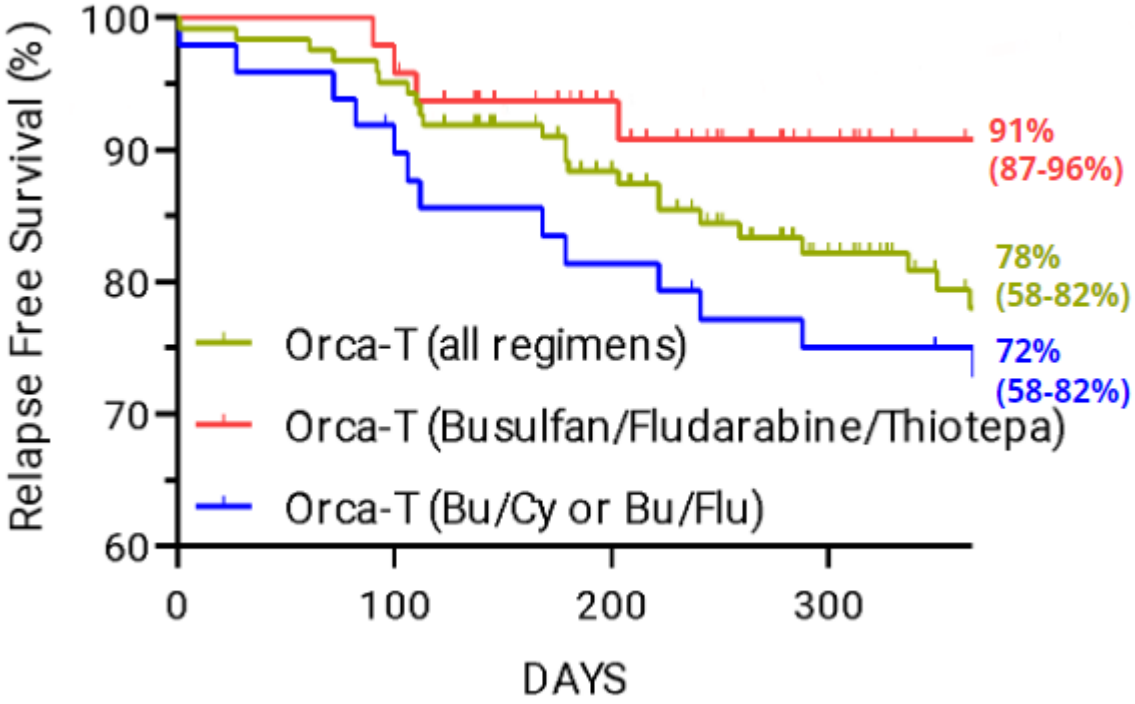
Chronic GVHD at 1 year was substantially reduced with Orca-T



Relapse at 1 year did not appear to be increased with Orca-T



Disease control with Orca-T may be further optimized by conditioning regimen choice



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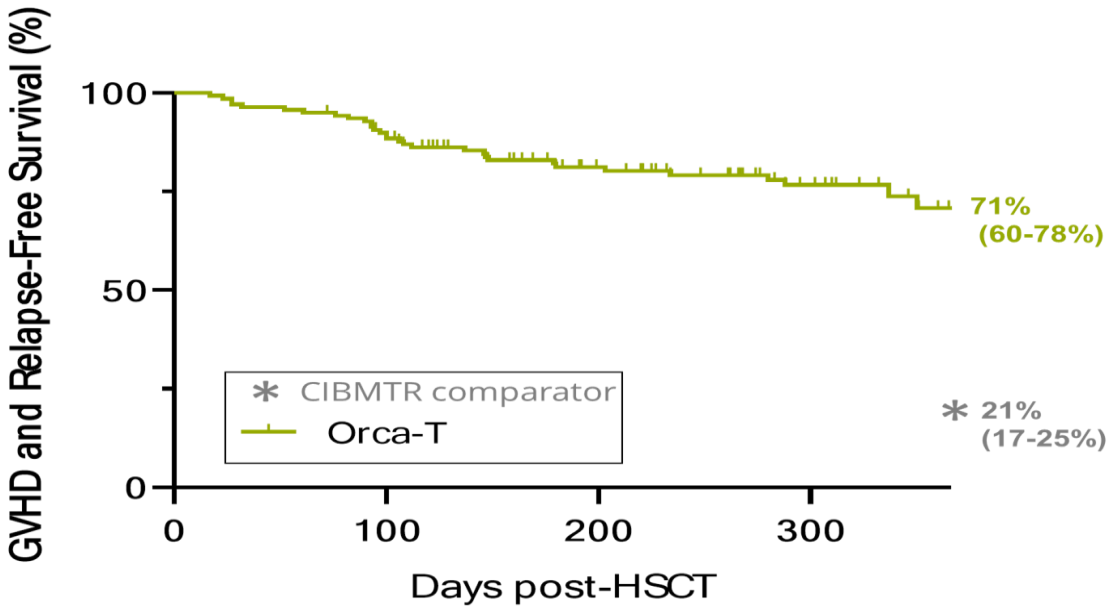
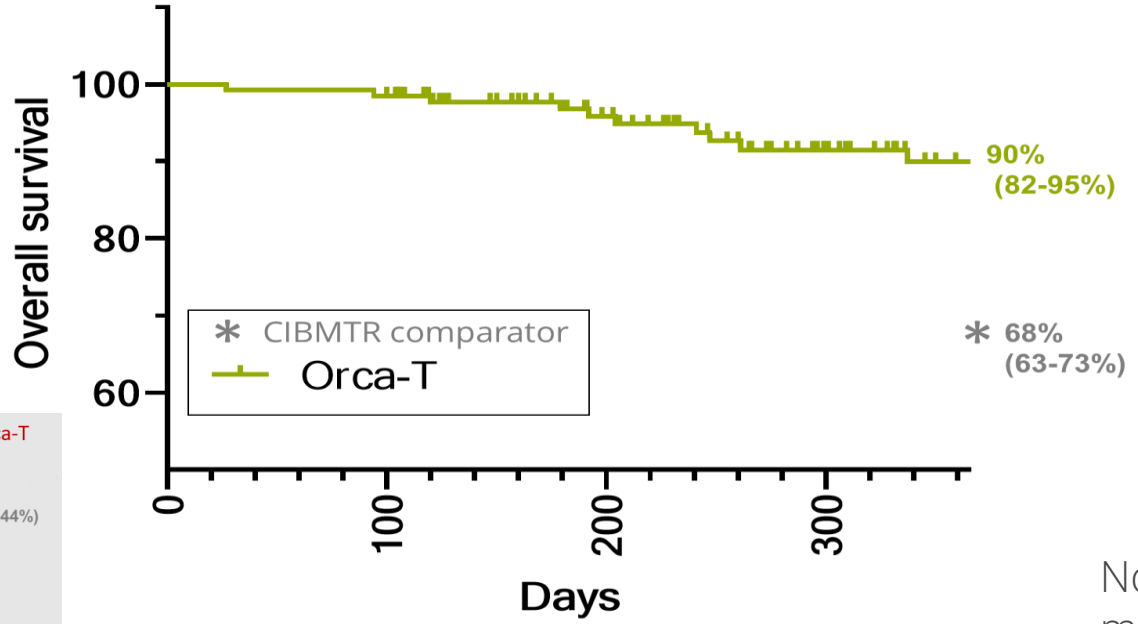
Orca-T can achieve a markedly improved GRFS

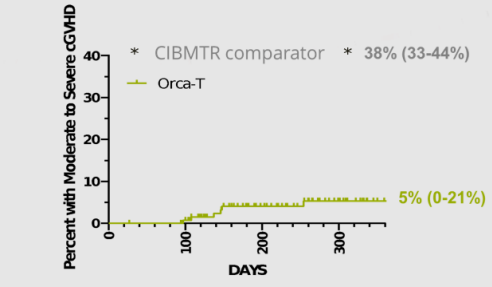


Orca-T may lead to overall improved survival without compromising QOL



Non-relapse mortality 4%

Chronic GVHD is substantially reduced with Orca-T



Precision-T: phase 3 pivotal trial for Orca-T

Phase 3 Trial is Currently Opening at Centers Across the US

Type of Trial:	• Randomized, multicenter study, blinded to sponsor
	• Target population: patients aged 18-65 with AML, ALL, or MDS planning to undergo allogeneic hematopoietic stem cell transplant
	• 1:1 randomization with patients receiving either:
	  • Orca-T plus single-agent tacrolimus or
	  • An unmanipulated allograft plus tacrolimus/methotrexate

Primary Endpoint:	Rate of survival free of moderate-to-severe chronic GVHD (“cGFS”)
Key Secondary Endpoint:	Relapse-free survival (“RFS”)
Trial Size:	~85 patients per arm
Duration:	• Trial completed when 57 events have occurred, where an event is defined as moderate-to-severe chronic GVHD or death

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Summary of experience with Orca-T to date

GRFS With Orca-T, 1-yr GRFS more than doubled with Orca-T compared to standard of care.

GVHD With Orca-T, significantly reduced acute and chronic GVHD compared to SOC despite reduction of immunosuppressive meds.

NRM Orca-T was well-tolerated with reduced non-relapse mortality.

GVI Improved time-to-engraftment compared to SOC. Low rates of severe infections post-transplant.

Central GMP laboratory production with no manufacturing/distribution failures => Vein-to-vein times of <72 hours across the continental United States.

Orca has initiated a Phase III study comparing Orca-T to standard-of-care allograft.

Participating Centers & Acknowledgements

- UC Davis Medical Center: Rasmus Hoeg, Mehrdad Abedi, Gerhard Bauer
- Oregon Health Sciences University: Arpita Ghandi
- UCLA Medical Center
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- Emory University: Ned Waller
- Medical College of Wisconsin: Bronwen Shaw
- Stanford Hospital and Clinics: Anna Pavlova, Lori Muffly, Parveen Shiraz, Sally Arai, Laura Johnston, Robert Lowsky Andrew Rezvani, Wen-Kai Weng, David Miklos, Matthew Frank, John Tamaresis, Ying Lu, Vaibhav Agrawal, Robert Negrin, Everett Meyer
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- Be The Match Biotherapies

Thank you to the patients who participated in these studies and to their families!

Thank you