Optimizing Outcomes with Myeloablative Conditioning in Older Patients: Efficacy and Safety of Orca-T in Patients ≥ 55 Years Old with Hematologic Malignancies

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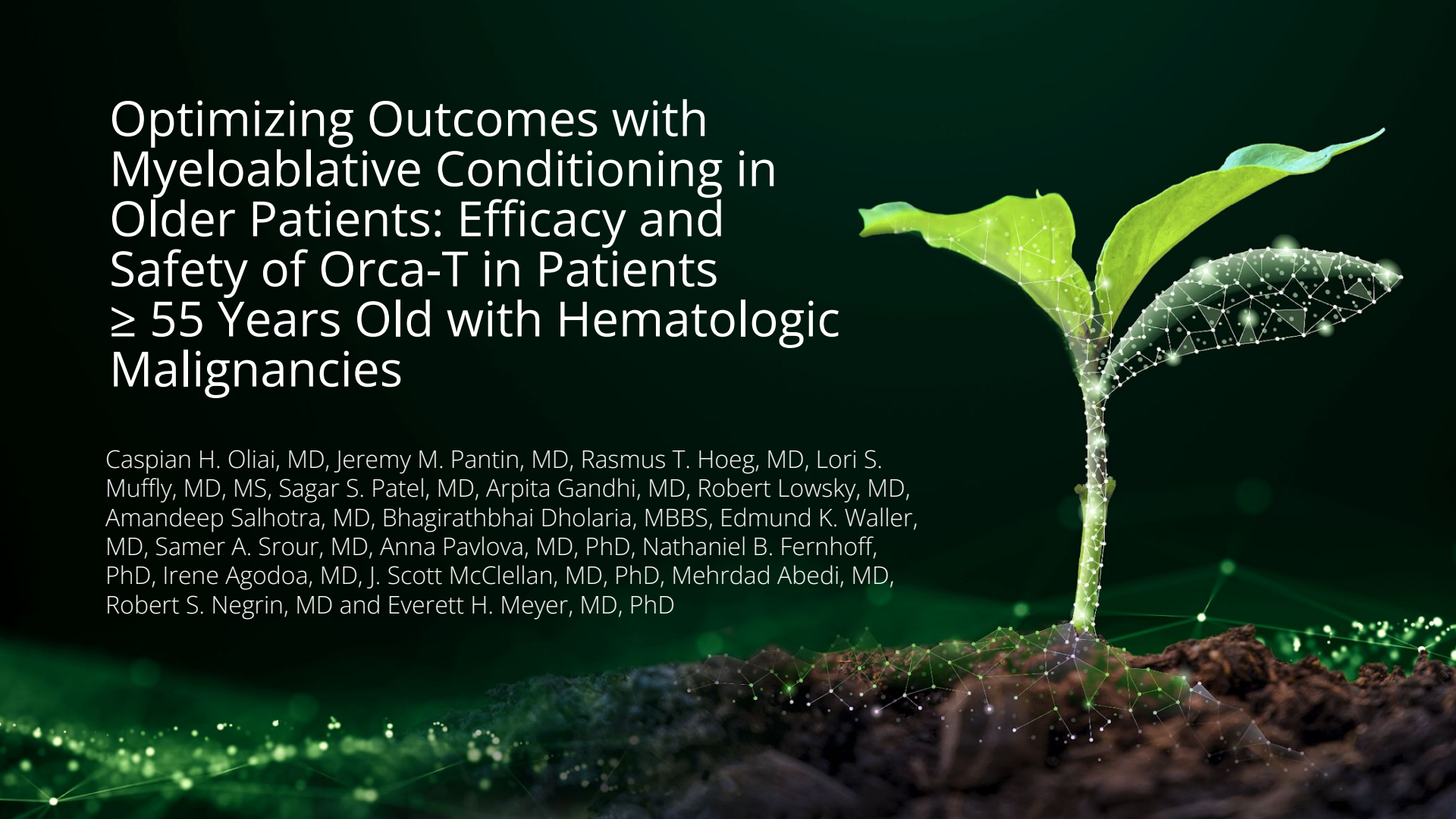
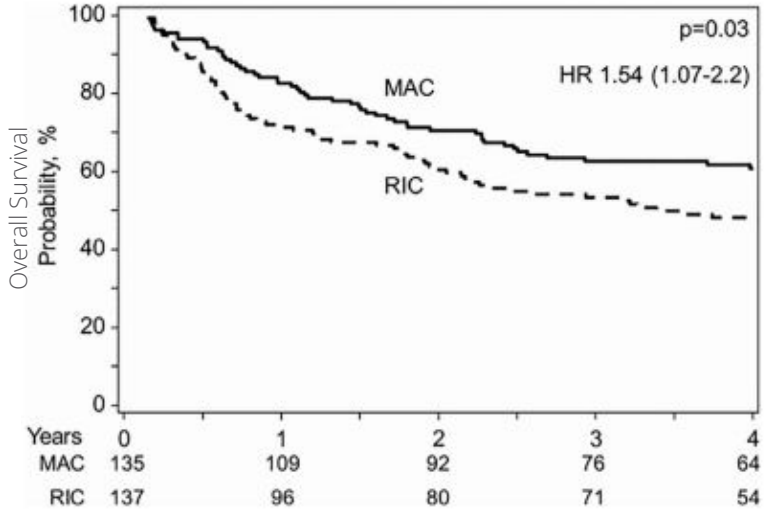


Myeloablative Conditioning Demonstrated a Survival Benefit vs Reduced Intensity alloHCT

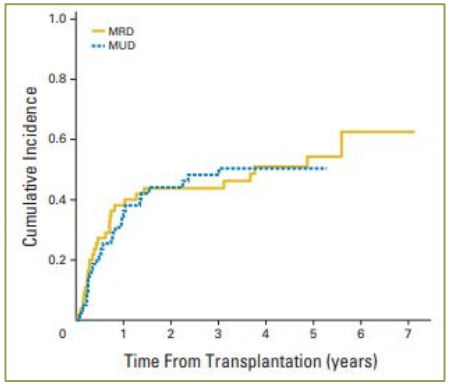
- BMT CTN 0901
  - MAC vs RIC for AML/MDS
  - Ages 18-65 yrs., MRD 6/6, MUD ≥ 7/8
- OS favored MAC
  - HR 1.5, p = .03
  - Relapse most common cause of death
  - RIC higher relapse, HR 4.0, p < .001
- TRM higher in MAC
  - 4 yr TRM 25% vs. 9% (HR 2.0, p < .001)



Scott et al. *Transplant Cell Ther*. 2021

Incidence of Relapse with RIC in Older Patients

- Phase II trial of alloHCT in 60-74 years old with AML in CR1
  - Alliance for clinical trials in Oncology / BMT CTN 0502
  - 114 patients with a median age of 65 years
- Cumulative incidence of relapse at 2 years = 44% (95% CI, 35% to 53%)



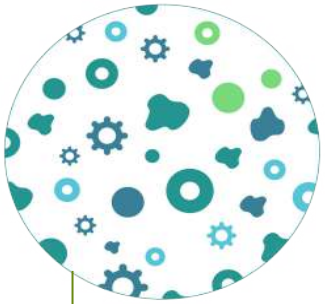
Devine et al. *J Clin Oncol*. 2015

- This demonstrates an unmet need to develop a strategy that lowers complications associated with TRM, without reducing the curative potential of MAC

Opportunity to Improve Clinical Outcomes from AlloHCT with Orca-T

Current Transplants

Uncontrolled mix of over 50 cell types
10e8 – 10e9 cells/kg



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

Orca-T

Defined Cell Population of Tregs and Tcons

(d0)

1 HSPC + Tregs 2

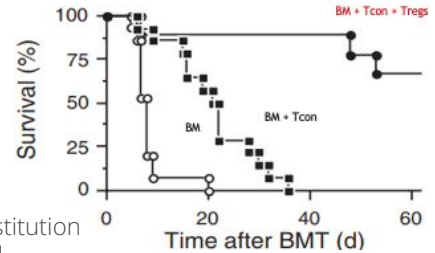
Long term blood and immune reconstitution

High purity to Prevent GvHD

(d+2)

3 Tcons

Bridge immune reconstitution
Disease control
Infection control

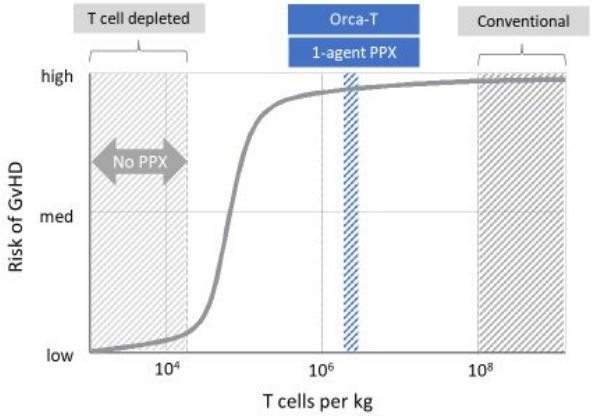


Edinger *et al*, 2003

HSPC, hematopoietic stem and progenitor cells; NK, natural killer

Orca-T is T Con Reduced and T Reg Purified

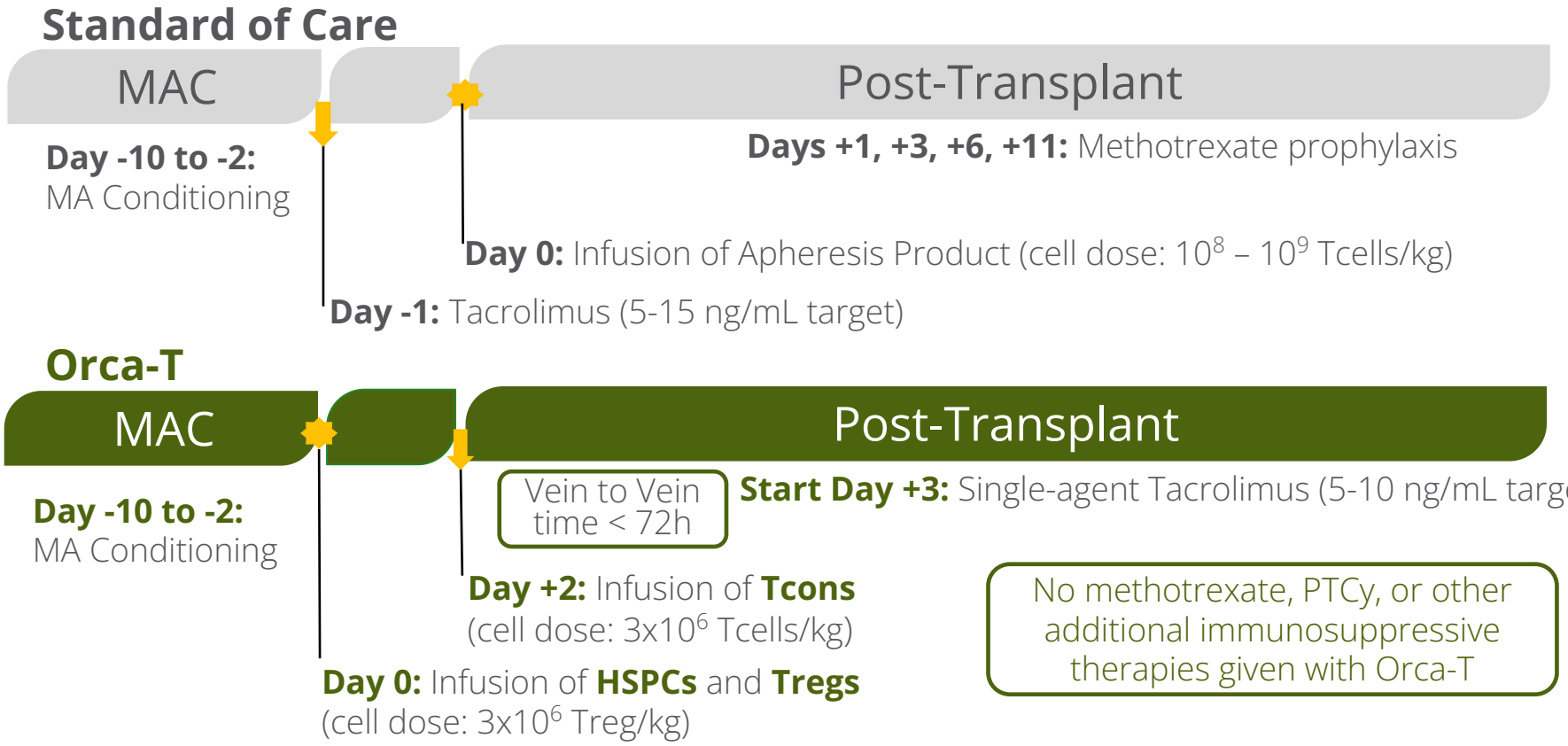
- Traditional T cell reduced grafts require GvHD prophylaxis with 2 agents
- Orca T utilizes a T cell reduced approach requiring only 1 agent GvHD prophylaxis



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

Treatment Comparison: SoC vs. Orca-T



Phase 1b Trial Analysis: Using Orca T in Older Patients Compared to Younger Patients

Multi-Center Phase 1b Single-Arm Trial*
• Acute leukemia (AML, ALL, mixed phenotype), in CR/CRi • Myelodysplastic syndrome • Chronic myeloid leukemia in chronic phase
• Age 18-75
• 8/8 matched related or unrelated donor
• HCT-CI ≤ 4
• KPS ≥ 70
• Adequate organ function
• Myeloablative regimen of IV busulfan (9.6 mg/kg IV), fludarabine (160 mg/m^2), and thiotepa (10 mg/kg) (BFT) • Single-agent GvHD prophylaxis with tacrolimus
• Primary endpoints: incidence of primary graft failure; incidence of severe aGvHD

*Patients with active disease or myelofibrosis were not included in this sub-group analysis

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CR, complete remission; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; HLA, human leukocyte antigen; KPS, Karnofsky performance Score.

Baseline Characteristics

Age group	18 to < 55 years old n = 39	≥ 55 years old n = 25
Median age	47	59
Median duration on study (months)	12	12
Female (%)	49	36
Ethnicity, Hispanic or Latino (%)	13	12
Baseline HCT-CI score (%)		
0	51	32
1	8	16
2	8	16
3	23	24
4	10	12
Primary Disease (%*)		
Acute lymphoid leukemia	8	12
Acute myeloid leukemia	74	44
Chronic myeloid leukemia	8	8
High-/very high-risk myelodysplastic syndrome	10	32
Mixed phenotype leukemia	0	4

Baseline Characteristics (ctd.)

Age group	18 to < 55 years old n = 39	≥ 55 years old n = 25
Matched (8/8 HLA) Donor Relationship		
Related	64	36
Unrelated	36	64
Measurable residual disease status (%)*		
Negative	64	48
Positive	31	24
DRI risk score		
High	8	40
Intermediate	79	52
Low	13	8

* evaluated at a central laboratory; based on flow cytometry

Results: Safety

- Median follow up: 12 months (range, 1.6 – 12)
- Graft failure: 1 younger patient
- Infections, grade 4 or 5
  - 0 younger patients
  - 3 older patients had grade 4
  - No grade 5 events
- Mucositis, grade 3
  - 1 younger patient
  - 1 older patient
  - No grade 4 or 5 events

Immune Reconstitution: T, B and NK Cell Counts

The median donor chimerism at 3 months was > 90% in both older and younger patients

Results: Graft vs Host Disease

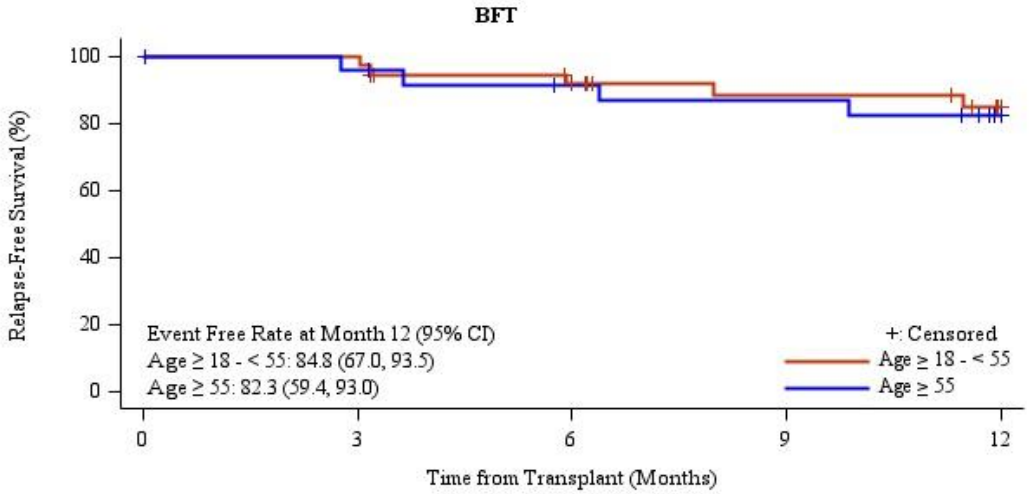
- Grade ≥ 3 acute GvHD
  - Younger patients: 0
  - Older patients: 1

- Moderate to severe chronic GvHD*
  - Younger patients: 3 moderate events
  - Older patients: 2 moderate, 1 severe event

* Median follow-up 12 months, scoring per NIH consensus criteria (Jagasia et al., 2015)

Jagasia et al., *Biol Blood Marrow Transplant* 2015; 21:389-401.

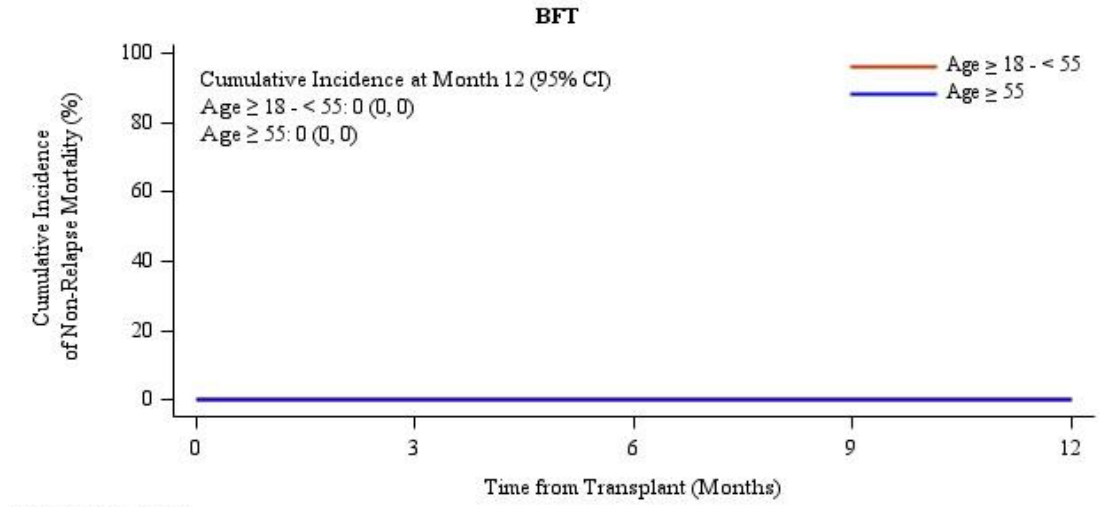
Relapse-Free Survival was Similar in Both Groups



Participants at Risk:

Age ≥ 18 - < 55	39	38	30	26	14
Age ≥ 55	25	23	20	19	13

NRM at 1-Yr Remained at Zero



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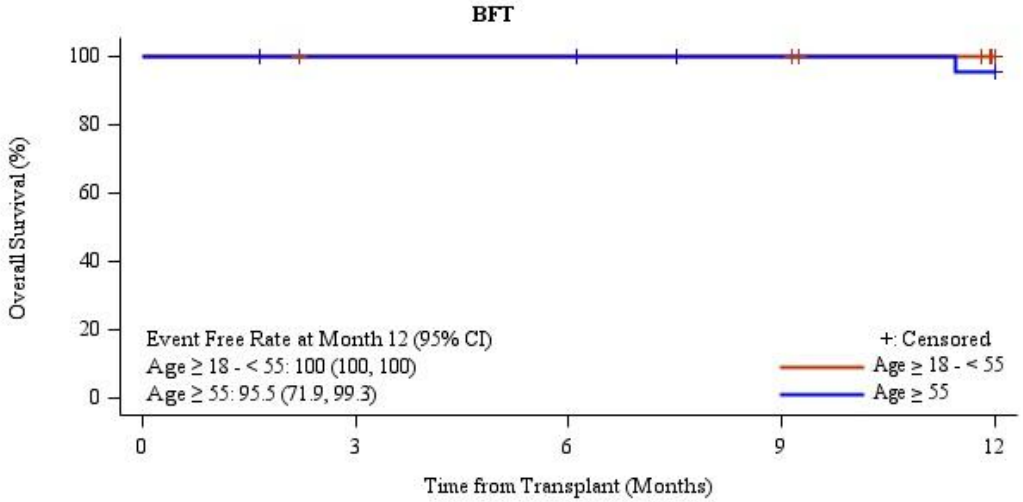
1-Yr Overall Survival in All Patients



Participants at Risk:

Age ≥ 18 - < 55	39	38	38	38	30
Age ≥ 55	25	24	24	22	21

Phase 3 Randomized Precision-T Study is Currently Enrolling

Orca Precision-T (NCT05316701)
• AML, ALL, MPAL, undifferentiated, in CR or CRi • Myelodysplastic syndrome (high-risk, therapy-related), including patients with active disease at time of transplant (≤ 10% BM blast burden)
Planned to undergo MA-alloHSCT including one of the following myeloablative conditioning regimens: • BFT • TBI/Etoposide • TBI/Cy
8/8 matched related or unrelated donor
HCT-CI ≤ 4
KPS ≥ 70
Age 18-65
Adequate organ function

Study arms
Experimental (n = 87)
Orca-T + single-agent Tac PPX
Active comparator (n = 87)
SOC (unmanipulated allograft) + dual-agent Tac/Mtx prophylaxis
Primary Endpoint
Chronic GvHD-free survival
Secondary Endpoint
GRFS, moderate-severe cGvHD, RFS

ALL, Acute lymphocytic leukemia, AML, acute myeloid leukemia; BFT, busulfan, fludarabine, and thiotepa; BM, bone marrow; cGVHD, chronic graft-versus-host disease; CR, complete remission; CRi, complete remission with incomplete count recovery; Cy, cyclophosphamide; GRFS, graft-versus-host and relapse-free survival; HCT-CI, hematopoietic cell transplantation comorbidity index; KPS, Karnofsky Performance Score; MPAL, mixed phenotype acute leukemia; Mtx, methotrexate; RFS, relapse-free survival; Tac, tacrolimus, TBI, total-body irradiation.

1. https://precisiontstudy.com/. Accessed 24Oct2022. 2. https://clinicaltrials.gov/ct2/show/NCT05316701. Accessed 24Oct2022.

Conclusions

- Orca-T has potential to be a reduced toxicity alternative to conventional allo transplant
- Using Orca T with myeloablative BFT conditioning has the potential to improve outcomes for older patients, based on > 95% overall survival and 1 year TRM of 0%
- An ongoing phase 3 trial evaluating Orca-T vs. standard of care is currently enrolling