A CD33-Deleted Allograft (Trem-cel) Enables Post-Hematopoietic Cell Transplant (HCT) Maintenance Dosing of Gemtuzumab Ozogamicin (GO) with Therapeutic Levels of Drug Exposure and Low Hematologic and Hepatic Toxicity in Patients with High-Risk Acute Myeloid Leukemia (AML).

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Disclosure Slide

John F. DiPersio

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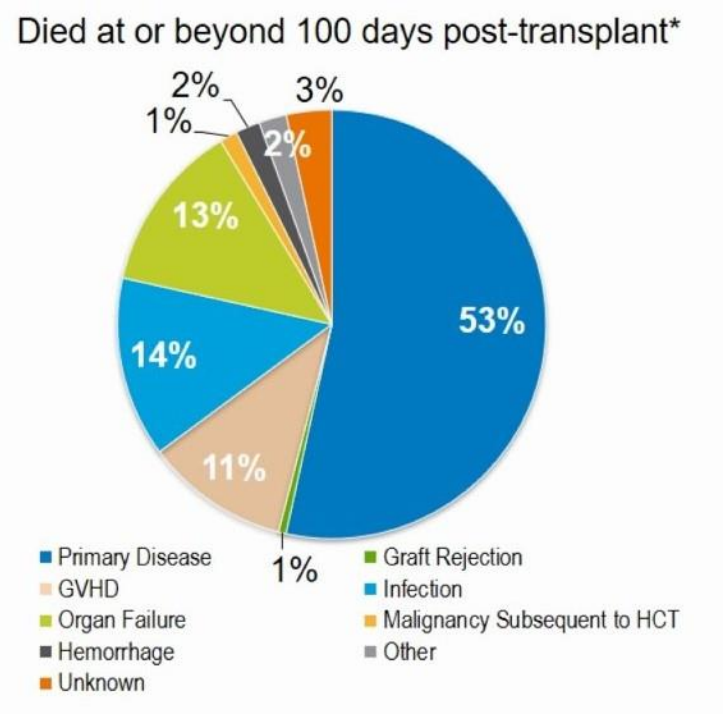
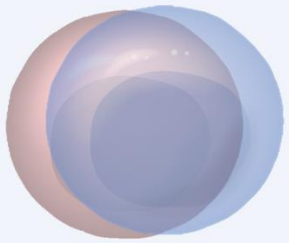
Enabling targeted therapies to reduce risk of relapse without hematotoxicity

Relapse is the leading cause of death post-alloHCT



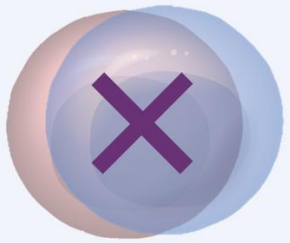
Adult unrelated donor HCT, CIBMTR 2020

Biology: Overlapping Targets



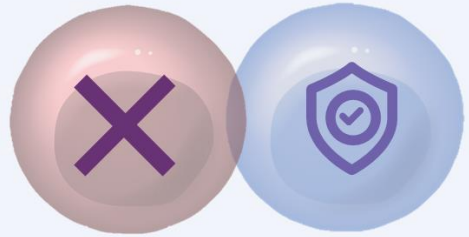
Cancer antigens also expressed on healthy cells

Problem: On-target Toxicity



Limits treatment opportunities leading to poor outcomes

Solution: Protected Transplants



Treatment-resistant transplants allowing therapies to be cancer-specific

CD33 as a Therapeutic Target

CD33 expression is dispensable

Expression highly restricted to hematopoietic compartment

Preclinical mouse models demonstrate comparable function and self-renewal of CD33-deleted HSPCs

Homozygous CD33 loss-of-function alleles present in humans without deleterious effects. (gnomAD database)

Targeting CD33 in AML

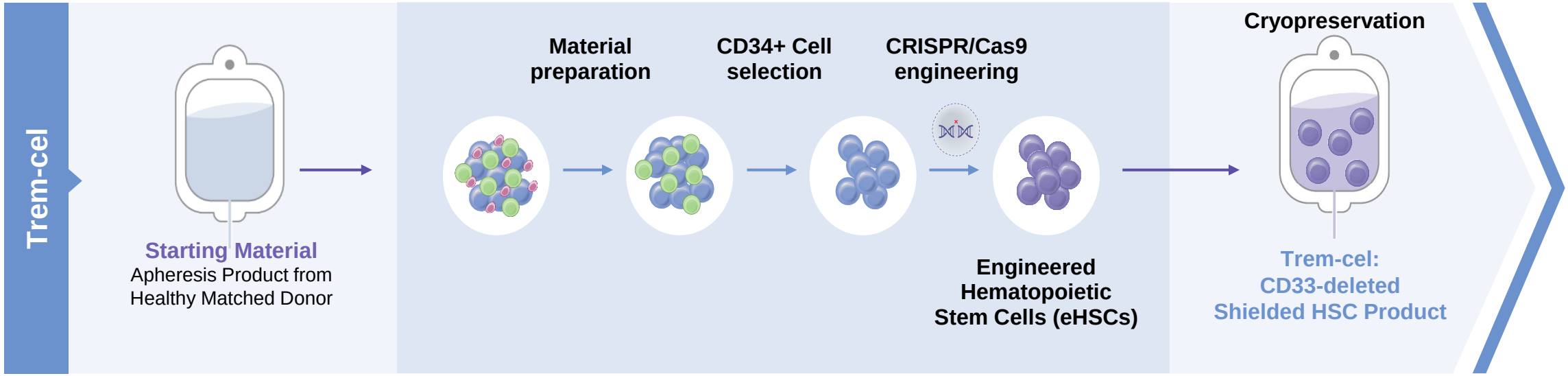
Expression in blast and LSC population of most AML cases

Gemtuzumab Ozogamicin (GO) is a CD33-directed ADC

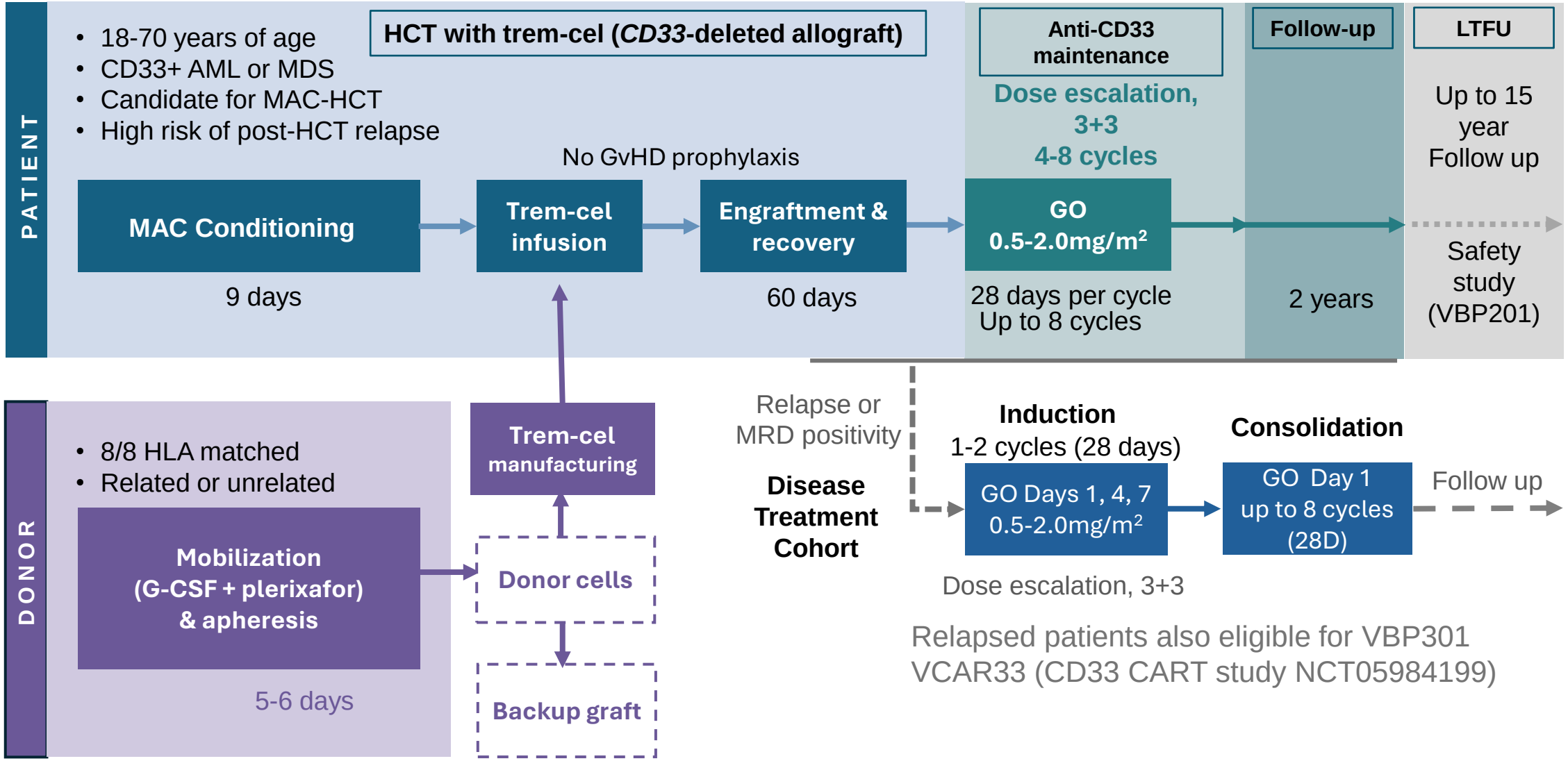
Major on-target hematotoxicity of neutropenia and thrombocytopenia

Use post-HCT limited by prolonged cytopenias

Trem-cel (VOR33): Using CRISPR/cas9-editing to delete CD33 in HSPCs



VBP101 Study Design



Clinicaltrials.gov NCT04849910

Patient Demographics and Disease & Graft Characteristics

Patient Demography (N=25)	
Age (years)	59 (22 – 68)
Sex	
Female	14 (56%)
Male	11 (44%)
Weight (kg)	72.6 (47.9 – 120.7)
Primary Disease Diagnosis	
AML	24 (96%)
MDS	1 (4%)
Trem-cel & Treatment Characteristics	
Trem-cel Cell Dose ($x10^6$ CD34+ cells/kg)	8.11 (2.62 – 12.44)
Editing Efficiency	90% (71– 94)
Donor Type (min 8/8 match)	
Unrelated	19 (76%)
Related	6 (24%)
10/10 match	25 (100%)
Myeloablative Conditioning Regimen	
Busulfan/ Melphalan/ Fludarabine/rATG	22 (88%)[a]
TBI/Cyclophosphamide/ Thiotepa/ rATG	3 (12%)
[a] One patient received equine ATG	

Disease Characteristics	
Cytogenetics Risk ELN 2022 (AML) | n=24	
Favorable	2 (8%)
Intermediate	8 (33%)
Adverse	14 (56%)
IPSS-R System (MDS) | n=1	
Very High	1 (100%)
Other AML Risk Factors | n=24	
TP53 mutation	8 (33%)
Secondary AML[b]	10 (42%)
[b] Defined as AML-MRC: AML with myelodysplasia-related change (9/24) or therapy-related (1/24)	
Disease Burden Status | N=25	
Remission (MRDneg)	18 (72%)
MRD+ (>0.1% to <5% blast by flow)	4 (16%) blast % range: 0.5% -3.6%
Active Disease (≥5% blast)	3 (12%) blast % range: 8% - 78%
AML/MDS Disease Status | N=25	
Primary induction failure	2 (8%)
CR1	16 (64%)
CR2	6 (24%)
Relapsed or refractory	1 (4%)

Values are median (range) or n (%)

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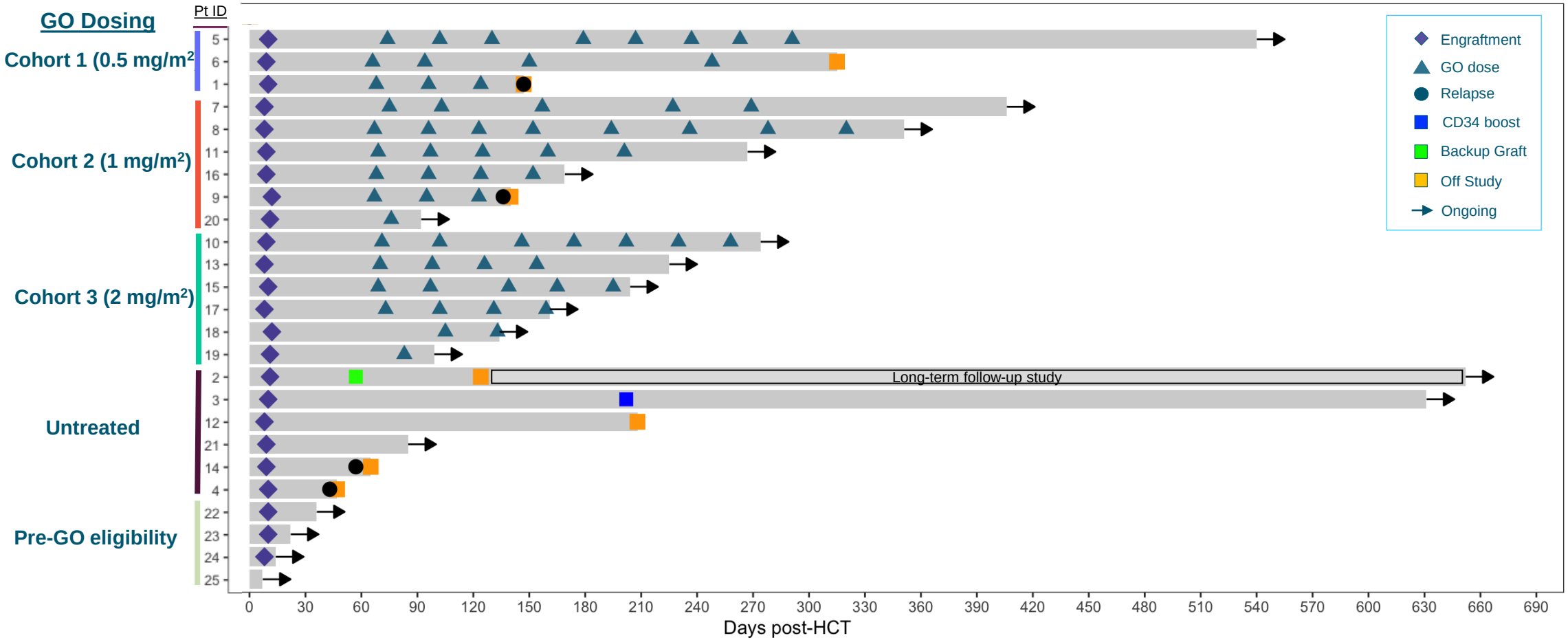
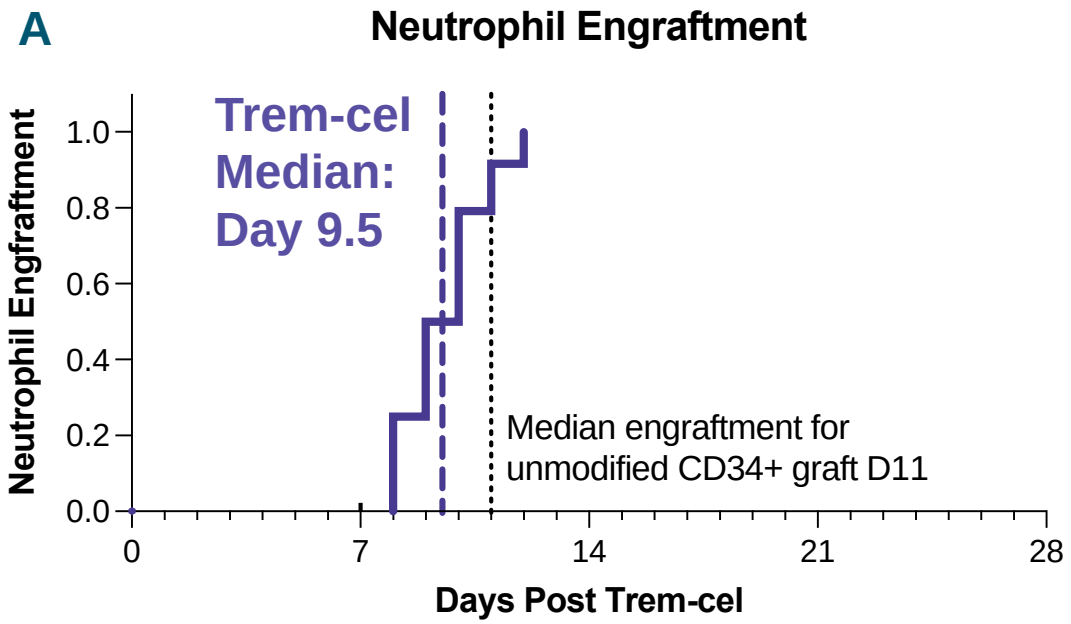
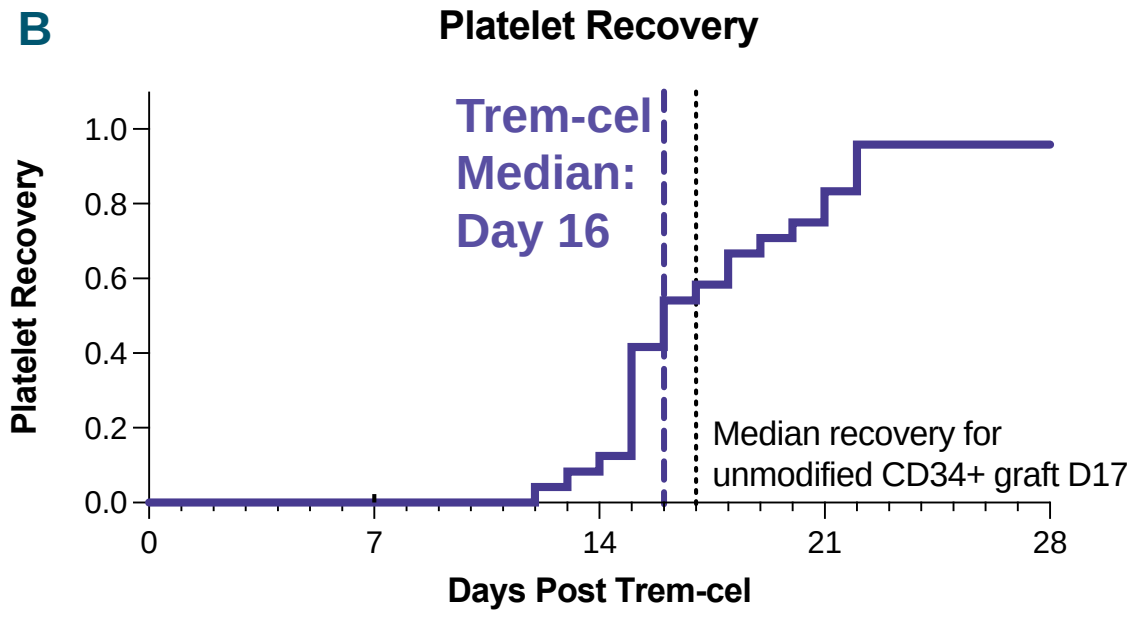
Patient Clinical Courses



Disposition of patients not treated with GO: Pt 2: Secondary graft failure with ongoing seasonal coronavirus infection. Recovered after unedited Backup graft
Pt 3: Delayed platelet recovery with anti-platelet antibody. Received unedited CD34 boost with recovery; Pt 12: Off study. Received DLI for viral infections
Pt 21: GO dosing delayed due to viral infection, ongoing; Pt 14: Relapse prior to GO eligibility; Pt 4: Relapse prior to GO eligibility

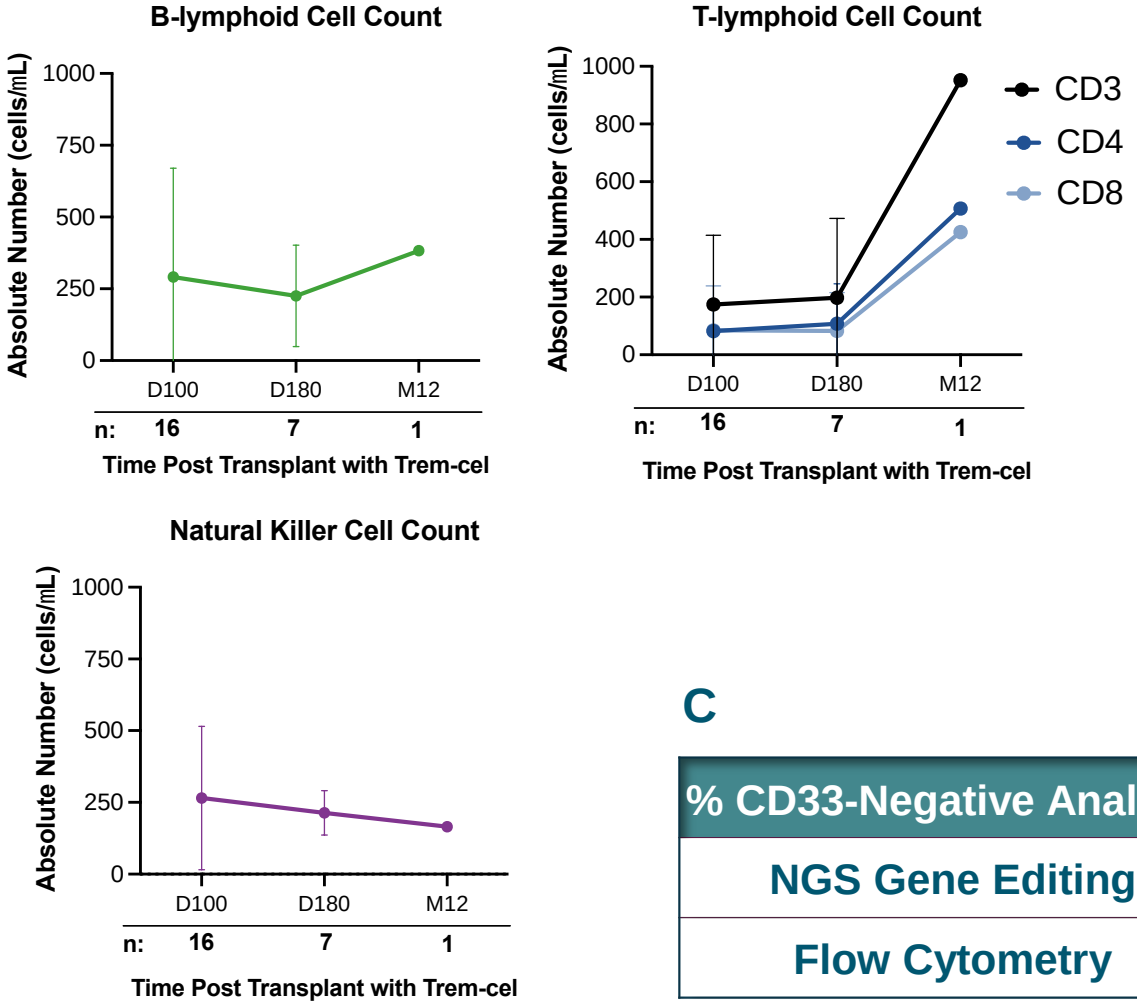
Neutrophil Engraftment and Platelet Recovery Post-HCT with Trem-cel are Similar to Unedited CD34-Selected Grafts



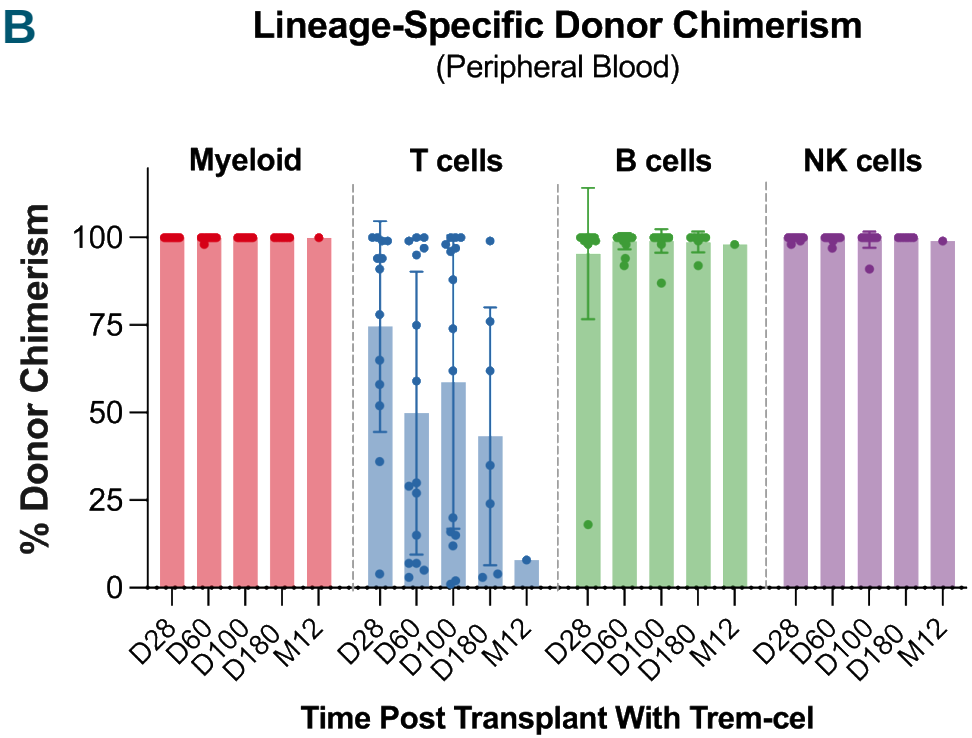


Immune Reconstitution, Full & Sustained Myeloid Chimerism, and CD33-negative Myeloid Cells Are Observed

A



B



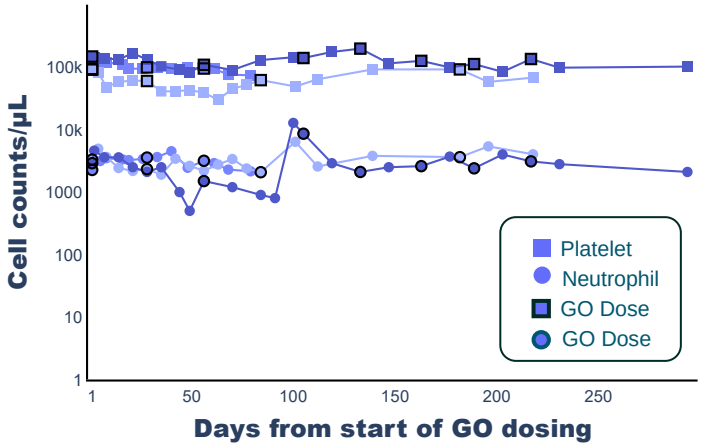
C

% CD33-Negative Analysis	Drug Product*	D28*	D60*
NGS Gene Editing	**90** (78-94) n=18	**94** (85-98) n=19	**94** (86-97) n=16
Flow Cytometry	N/E	**93** (74-98) n=22	**94** (78-99) n=19

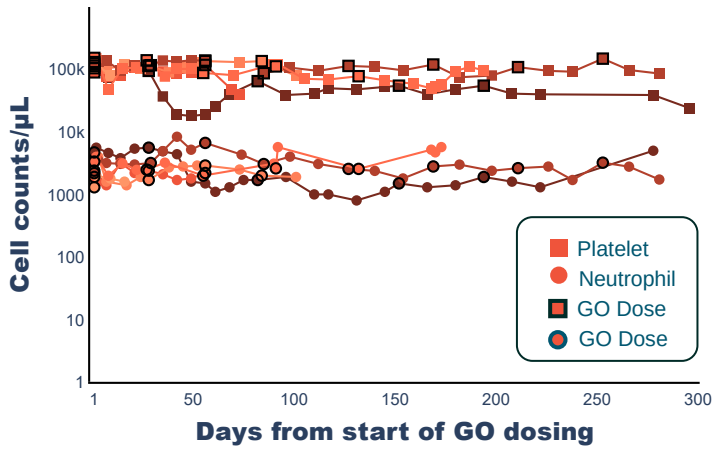
*Mean % (range), Editing and flow data from peripheral blood monocytes and myeloid cells respectively
N/E: not evaluated

Trem-cel Provides Hematologic Protection and Enrichment of CD33-negative Myeloid Cells upon GO Dosing

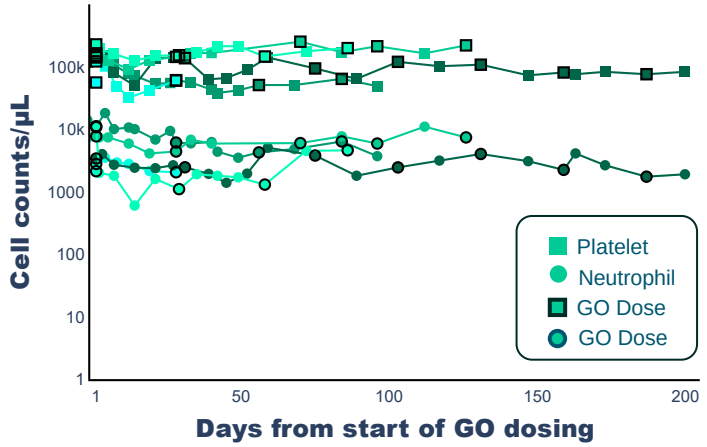
A Cohort 1 (0.5 mg/m^2) n=3



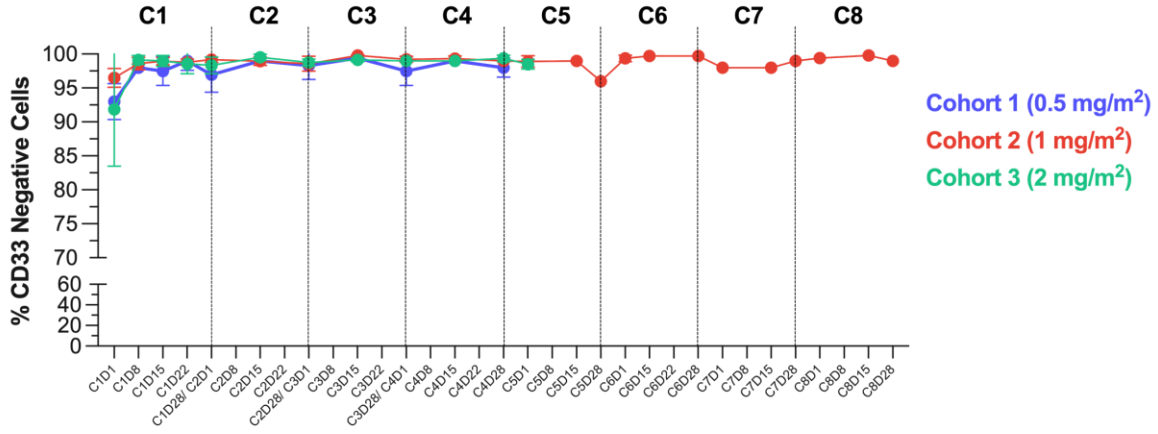
B Cohort 2 (1 mg/m^2) n=6



C Cohort 3 (2 mg/m^2) n=6



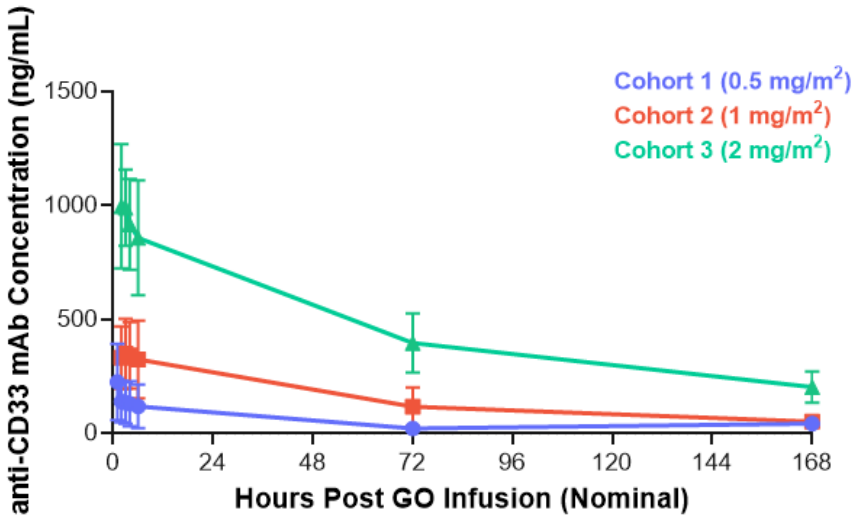
D Loss of CD33 Expression on PB Myeloid Cells n=15



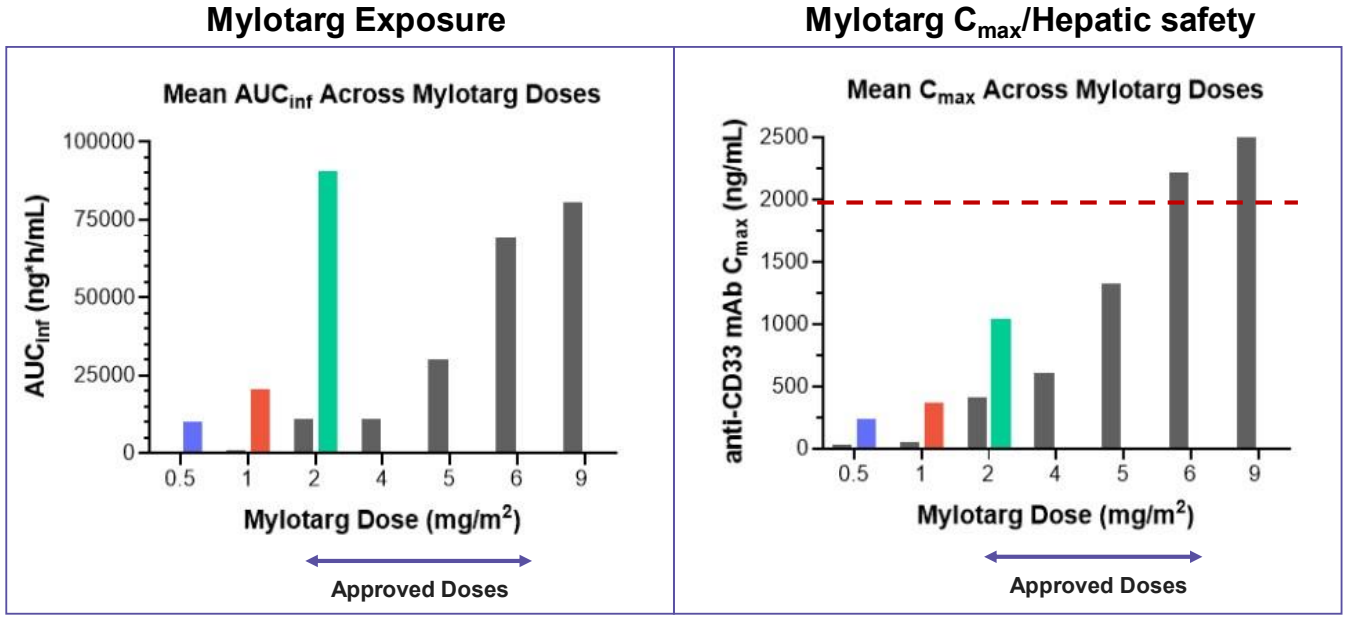
Cohort 1 (0.5 mg/m^2)
Cohort 2 (1 mg/m^2)
Cohort 3 (2 mg/m^2)

Safety and Efficacy at Lower GO Dose in CD33-Negative post-Trem-cel HCT Setting

A



B



Blue/Red/Green Bars: VBP101; Grey bars: Mylotarg PK Analysis; Red dashed line: Risk of hepatic SOS/VOD ~5 %[2]

(A) First dose GO Pharmacokinetic profile of 3 dose cohorts. (B) First dose Mylotarg (GO) exposure (AUC_{inf}) (Left panel) and C_{max} (right panel) compared to first dose Mylotarg PK values in R/R AML patients (FDA ODAC 2017)

Note: some AUC_{inf} values may fall outside 20 percent extrapolation.

Treatment Emergent Hematologic and Hepatobiliary Adverse Events in Patients (n=15) After Receiving GO (Highest Grade)

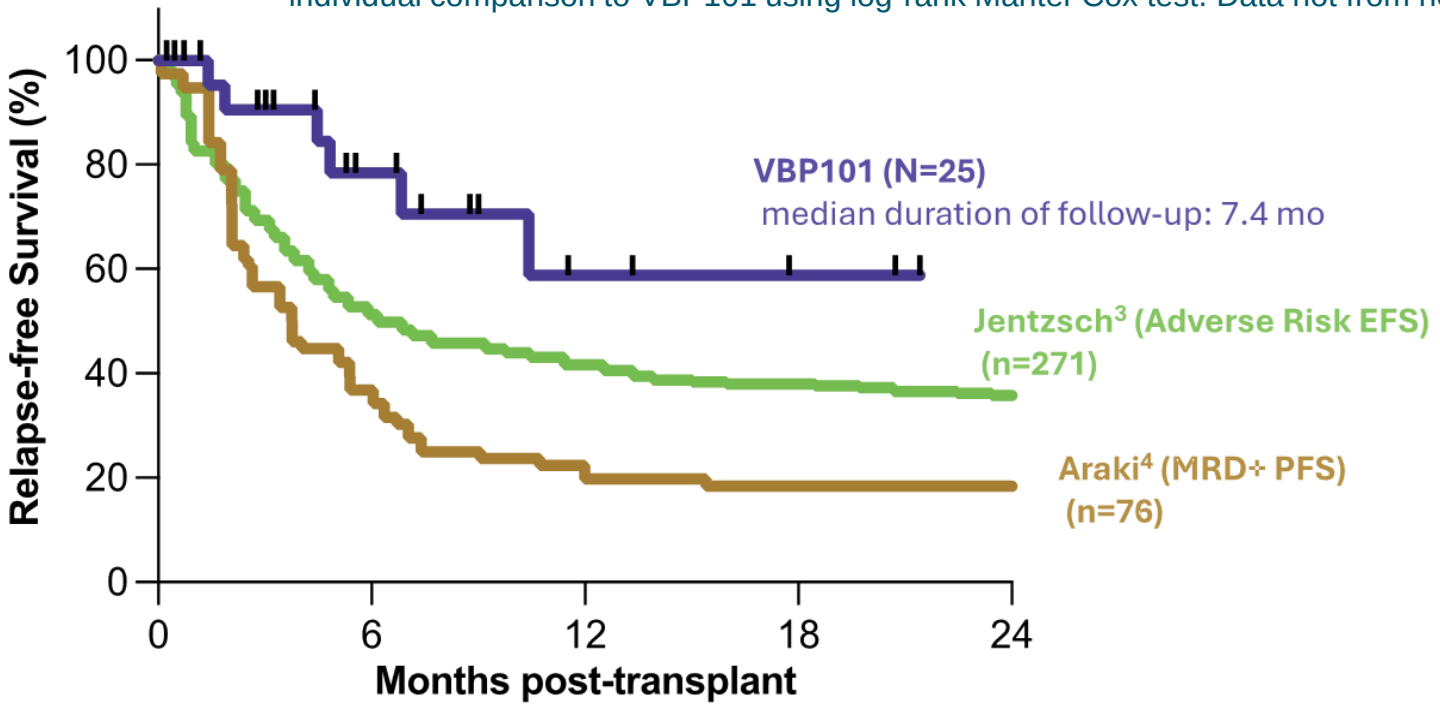
Adverse Event	Gr1	Gr2	Gr3	Gr4	Gr5
Hematologic					
Anaemia	-	1/15 (7%)	3/15 (20%)	-	-
Autoimmune haemolytic anaemia	-	-	1/15 (7%)	-	-
Leukopenia	-	-	1/15 (7%)	-	-
Lymphocyte count decreased	1/15 (7%)	-	-	-	-
Lymphopenia	-	-	1/15 (7%)	-	-
Neutropenia	-	2/15 (13%)	3/15 (20%)	-	-
Platelet count decreased	-	-	2/15 (13%)	-	-
Thrombocytopenia	-	1/15 (7%)	1/15 (7%)	1/15 (7%)	-
Hepatobiliary					
ALT increased	2/15 (13%)	1/15 (7%)[a]	-	-	-
AST increased	1/15 (7%)	-	1/15 (7%)[a]	-	-
Biliary colic	1/15 (7%)	-	-	-	-
Alk Phos increased	3/15 (20%)	-	-	-	-
Blood bilirubin increased	1/15 (7%)	-	-	-	-
LDH increased	2/15 (13%)	-	-	-	-
Cholecystitis	-	2/15 (13%)	-	-	-
VOD	1/15 (7%)[b]	-	-	-	-

[a]ALT/AST elevation attributed to fluconazole toxicity and resolved after discontinuation
[b]mild late onset SOS/VOD occurred 97 days after 0.5 mg/m2 GO dose. Predisposing factors included azole toxicity, concurrent Norovirus infection and gram negative bacteremia.
ALT, Alanine aminotransferase; AST, Alanine aminotransferase; Alk Phos, blood alkaline phosphatase; LDH, blood lactate dehydrogenase
VOD, veno-occlusive disease of the liver

Relapse-free Survival of VBP101 patients compared to typical adverse risk genetics or MRD+ populations

Study	Median RFS (mo)	P value vs. VBP101	Hazard Ratio* (HR)	HR 95% CI*
VBP101	Not reached			
Jentzsch	6.2	0.02	0.44	0.25 – 0.77
Araki	3.8	0.001	0.28	0.17 – 0.48

* individual comparison to VBP101 using log-rank Mantel-Cox test. Data not from head-to-head trial.



- Four relapses observed: (all CD33 positive at relapse)
  - 3/4 transplanted with active disease; 1/4 with MRD
  - 4/4 Adverse risk cytogenetics
  - 2/4 relapsed prior to GO treatment
- One patient died off-study due to complications of viral infection, one patient off-study due to DLI use for viral infection

Conclusions

Patients transplanted with trem-cel on VBP101 show:

- ❑ **Primary neutrophil engraftment and platelet recovery and full donor myeloid chimerism similar to patients who received non-edited CD34 selected grafts, consistent with CD33 being dispensable for engraftment and hematopoiesis.**
- ❑ **Protection from deep and prolonged cytopenias during repeated 0.5, 1, and 2 mg/m^2 GO doses.**
- ❑ **Immune reconstitution and multilineage chimerism consistent with unedited CD34-selected grafts.**
- ❑ **Broadened therapeutic index for GO following trem-cel as demonstrated by increased AUC, correlated with efficacy, and proportionally lower increase in Cmax, correlated with hepatotoxicity, compared to corresponding GO doses in R/R AML patients.**
- ❑ **Preliminary data suggesting improved RFS compared to standard HCT of AML high-relapse risk groups.**

Dose Escalation Committee determined Recommended Phase 2 Dose of GO as 2 mg/m^2

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Vor Bio

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The patients, donors, and their families and caregivers