Trem-cel, a CRISPR/Cas9 gene-edited allograft lacking CD33, shows rapid primary engraftment with CD33-negative hematopoiesis in patients with high-risk AML and avoids hematopoietic toxicity during gemtuzumab ozogamicin (GO) post-hematopoietic cell transplant (HCT) maintenance.

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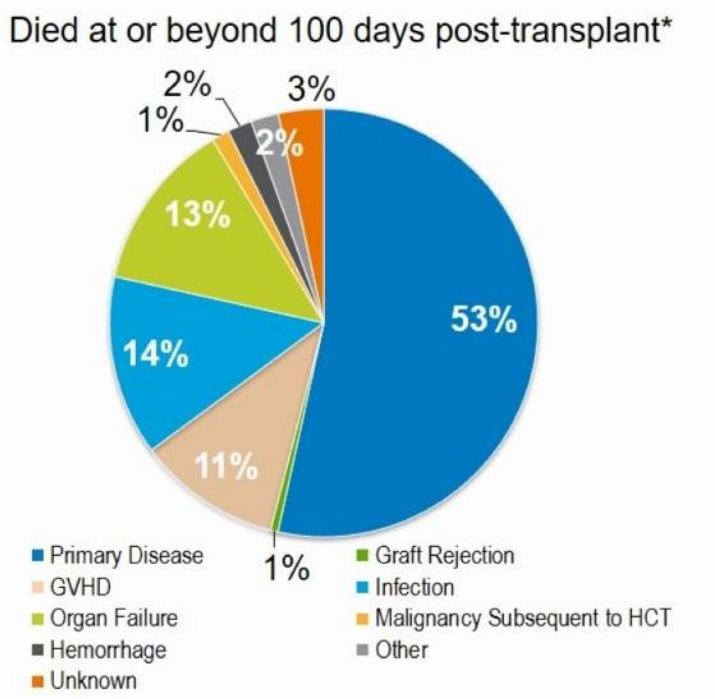
November 10th, 2023
Relapse after HSCT2

Disclosures

I have no relevant disclosures

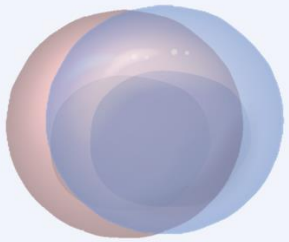
Enabling targeted therapies to reduce risk of relapse without hematotoxicity

Relapse is the leading cause of death post-alloHCT



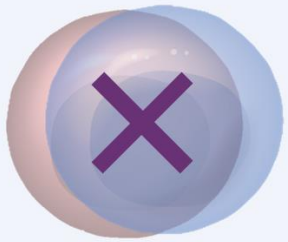
Adult unrelated donor HCT, CIBMTR 2020

Biology: Overlapping Targets



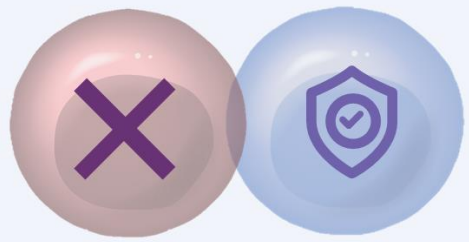
Cancer antigens also expressed on healthy cells

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

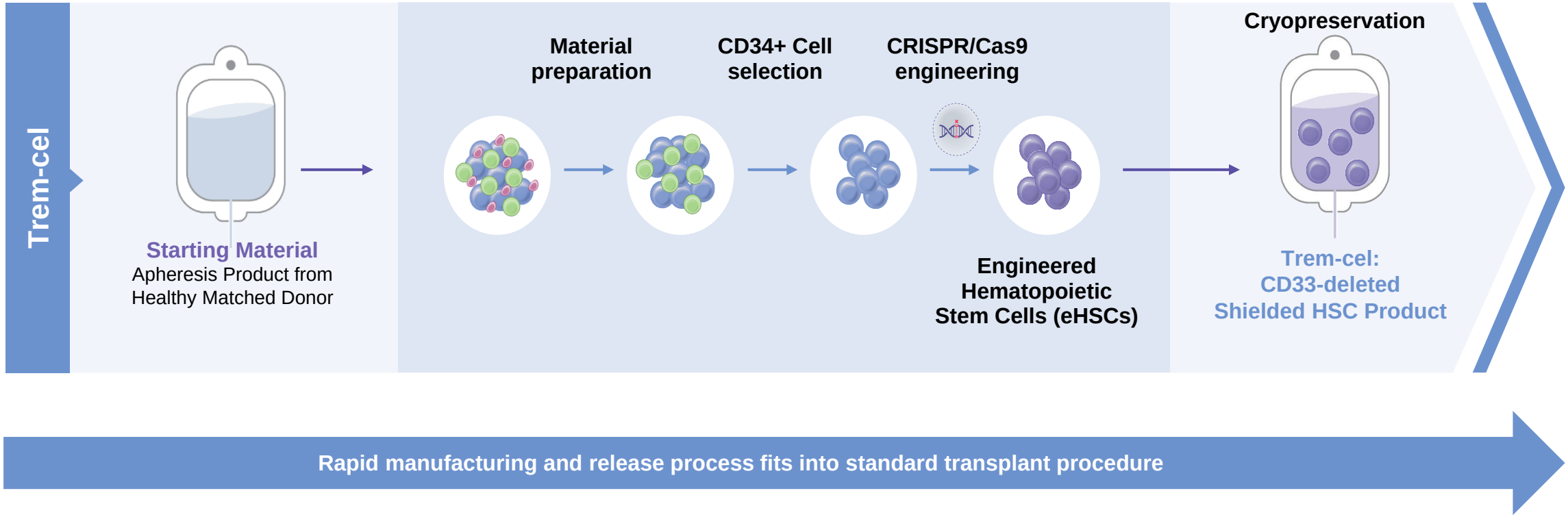
CD33 expression is dispensable

- 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)

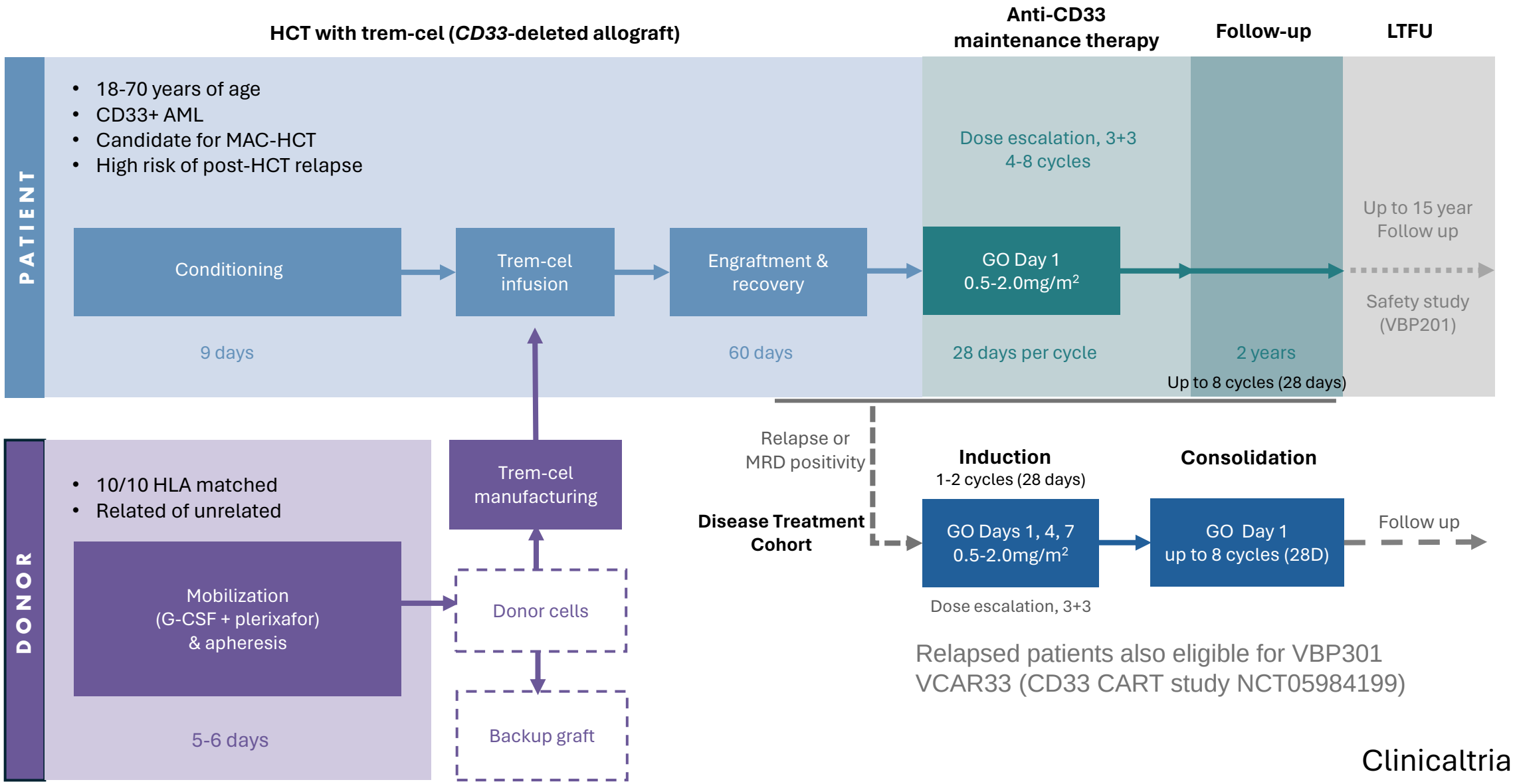
Targeting CD33 in AML

- Expression in blast and LSC population of most AML cases
- Gemtuzumab Ozogamicin (GO; Mylotarg™) 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 Trial Schema



Relapsed patients also eligible for VBP301 VCAR33 (CD33 CART study NCT05984199)

Clinicaltrials.gov
NCT04849910

VBP101 Eligibility and Endpoints

Key Eligibility

CD33+ AML

Age 18-70y

10/10 HLA-matched donor

- related/unrelated

MAC candidate

Relapse risk factors

- i.e. MRD+, Adverse genetics, CR2

Endpoints

Primary Endpoint

- Incidence of primary neutrophil engraftment by Day 28

Secondary Endpoints include:

- Time to neutrophil/platelet recovery
- Safety of trem-cel and GO
- MTD & Rec Phase 2 Dose of GO
- RFS, OS, CI of relapse

Patient and trem-cel graft characteristics

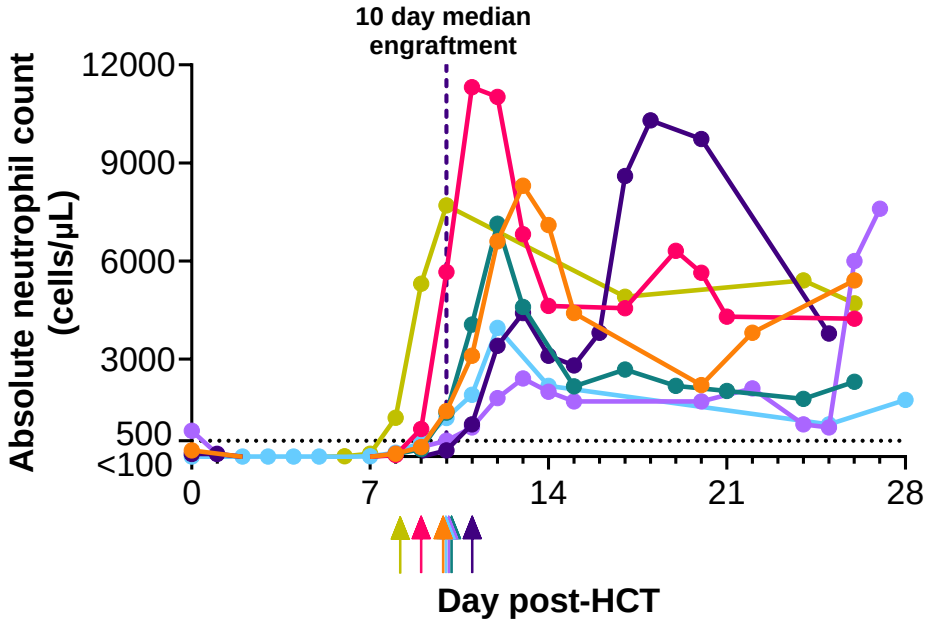
Pt	Age/ Sex	AML & Risk Factors	Weight	10/10 Donor	Dose (×10^6 CD34 cells/kg)	CD33 Gene Editing
1	64/F	AML with MDS related changes highly complex (adverse) cytogenetics, CR2, Mutant TP53 MRD: 1.8%	69.9 kg	Unrelated	7.6	88%
2	32/M	AML persistent myeloid sarcoma Inv 16 and +22; t(3;3)	120.7 kg	Unrelated	3.2	87%
3	55/F	AMLwith MDS related changes Mutant DNMT3A, IDH2 and SMC1A	114.1 kg	Unrelated	2.6	80%
4	68/M	AML with MDS related changes Complex cytogenetics NRAS, ZRSR2, TET2 mutations 16% blasts	72.4 kg	Related	5.8	89%
5	66/M	Secondary AML KIT D816V, CBL, SRSF2, RUNX1/2, BCORL1 mutations	102.1 kg	Unrelated	4.6	85%
6	63/F	AML with MDS related changes Complex cytogenetics Mutant TP53	66.2 kg	Unrelated	5.7	91%
7	67/F	AML with recurrent abn. NPM1, TET2, EZH2, PIGA, SETBP1 mutations, CR2	72.8 kg	Unrelated	9.4	87%

All patients received myeloablative conditioning with busulfan/melphalan/fludarabine/rabbit anti-thymocyte globulin (ATG), with exception for patient #3, who received equine ATG.

Data Cutoff: 31 Oct 2023. Presented data from EDC and site/PI communication; pending full source verification

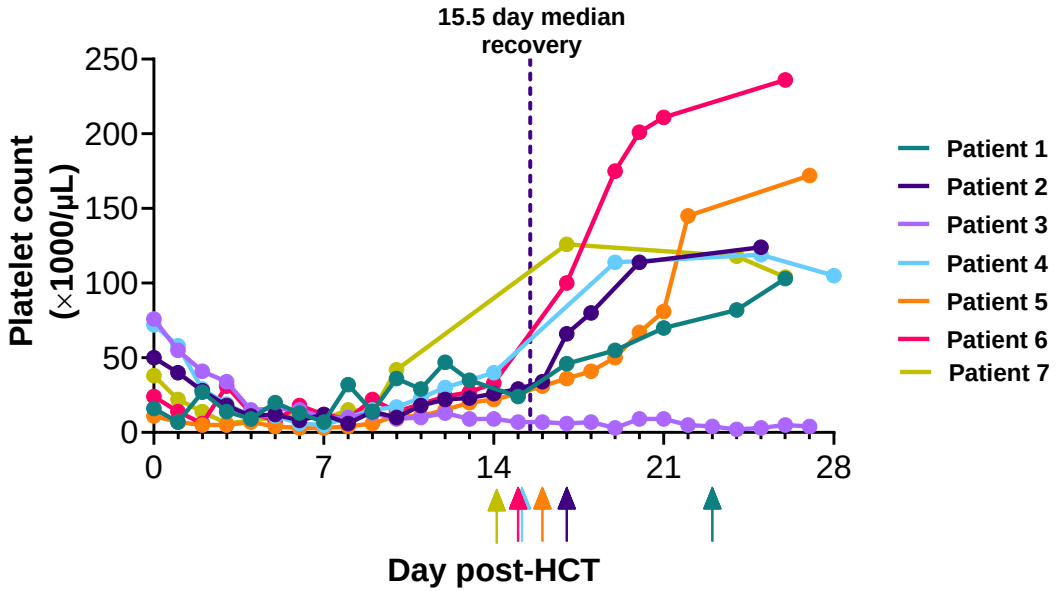
Neutrophil engraftment and platelet recovery are similar to unedited CD34-selected grafts*

Neutrophil Engraftment



Arrows indicate days of individual patient engraftment

Platelet Recovery

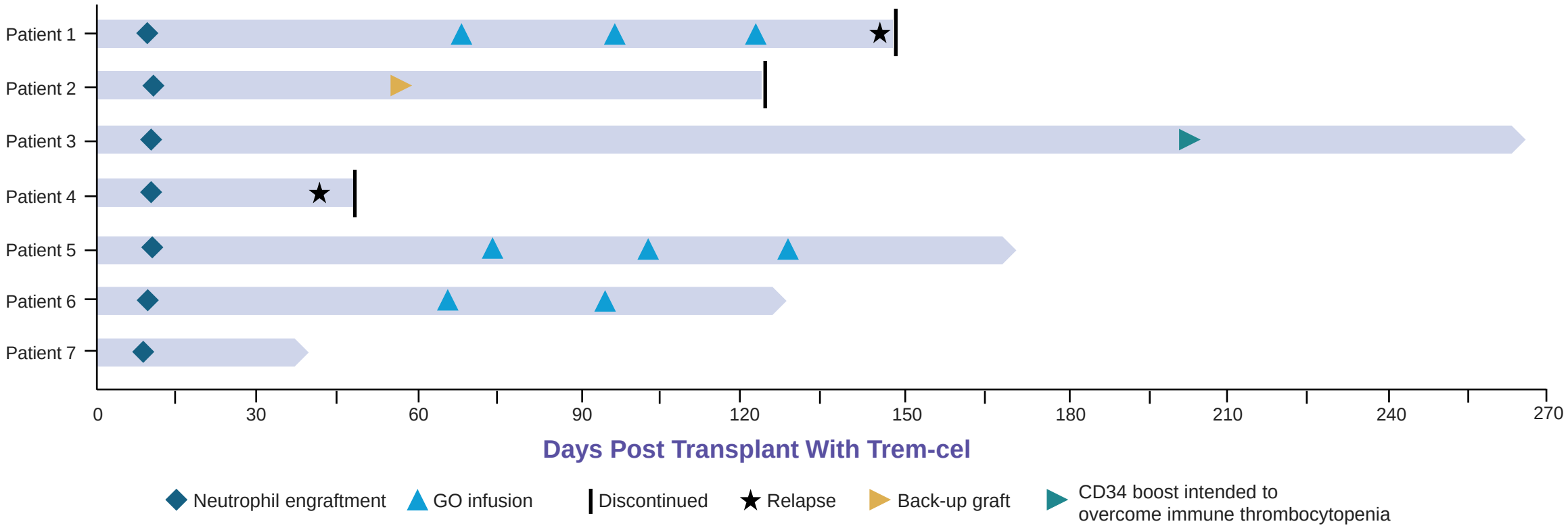


Median excluding pt 3 with immune thrombocytopenia

Full Myeloid Chimerism in all patients at D+28

* (Luznik et al JCO 2021: CD34-selected grafts neutrophil engraftment median 11 days & platelet recovery 17 days)

Patient Clinical Timelines (Patients 1-7)



Patients Ineligible for GO:

Patient 2

Secondary graft failure in context of prior sepsis, TMP-SMZ/possible DRESS and persistent hKU1 Coronavirus infection. Graft failure resolved after back-up graft given.

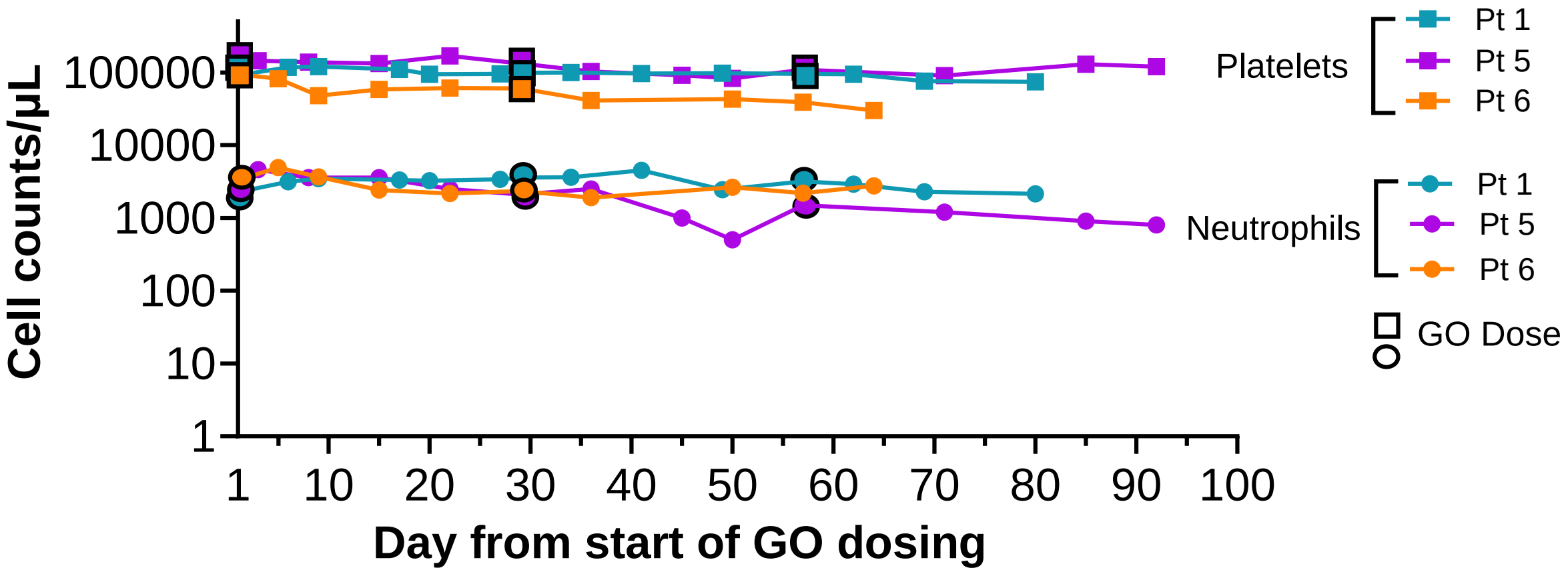
Patient 3

Immune thrombocytopenia. Resolving after treatment with IVIg, steroids, rituximab, CD34 boost.

Patient 4

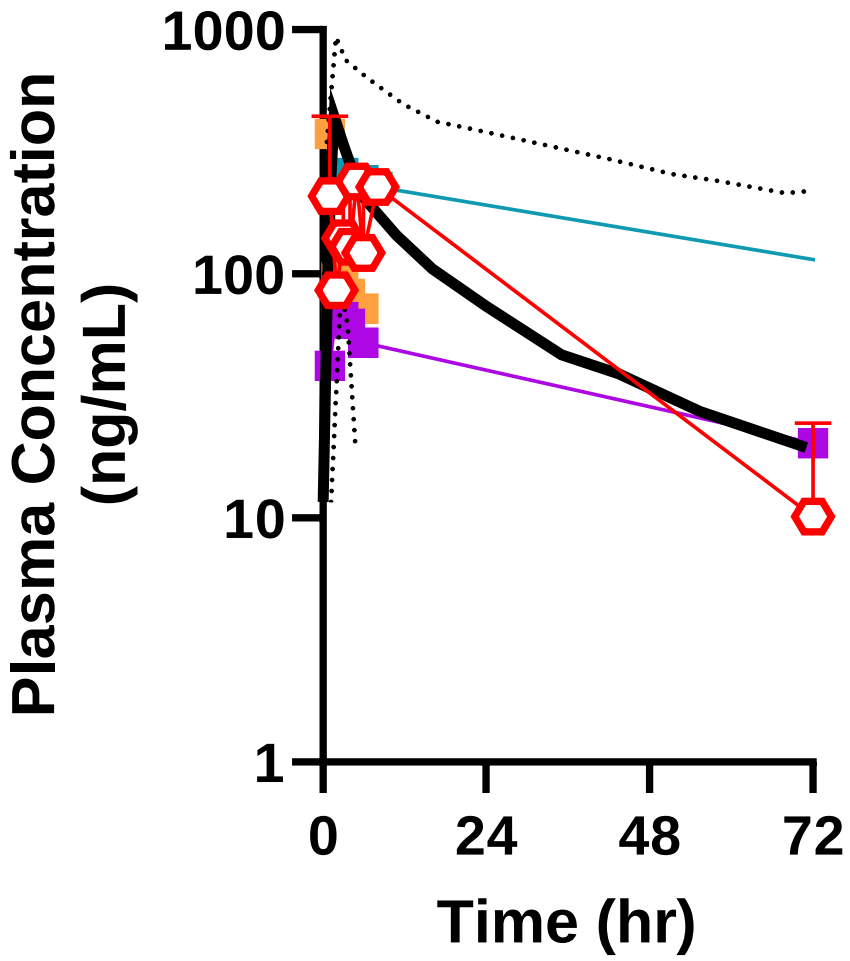
CNS and systemic relapse prior to GO dosing.

Neutrophil and platelet counts after GO dosing: Cohort 1 (0.5 mg/m^2)



GO C1 Start: Pt 1 D+68; Pt 5 D+74; Pt 6 D+66 post-HCT

Pharmacokinetic Data: Cohort 1 (0.5 mg/m²)
Higher GO exposure in the context of CD33-negative hematopoiesis



R/R AML — Mean 3.0 mg/m^2
2.5% CI
97.5% CI

VBP101 — Mean 0.5 mg/m^2 (SD)
Patient 1
Patient 5
Patient 6

Mean (SD) Exposure Parameters:

C_{max} (ng/mL): 235.9 (+/- 151)

AUC_{last} (ng*hr/mL): 8857 (+/- 12355)

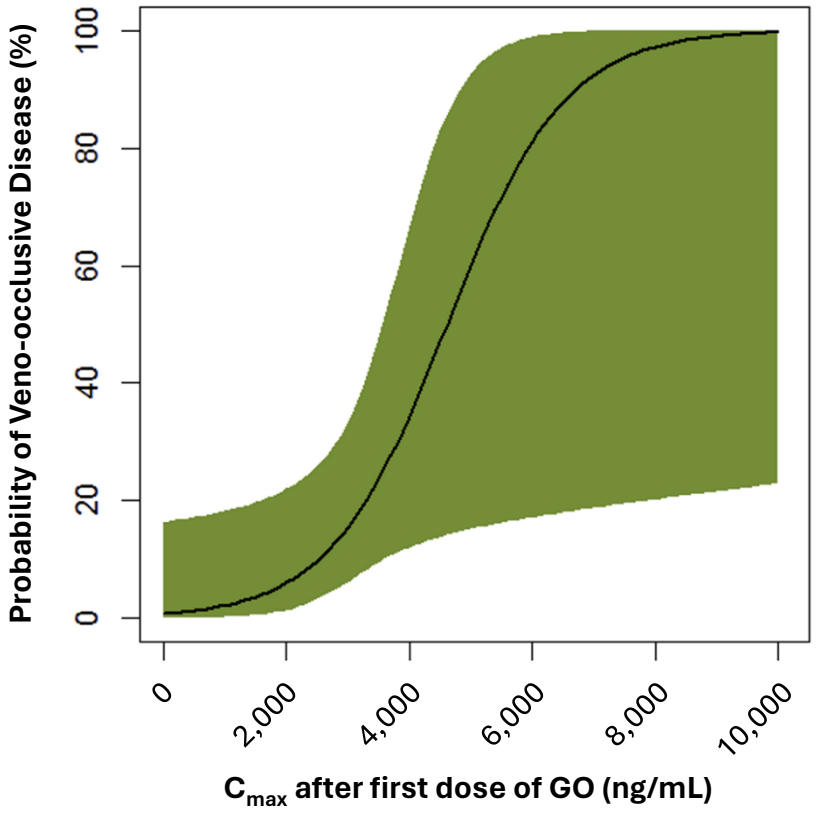
Data from 3.0 mg/m^2 Mean (+/- CI) Data Digitized from Simulations Presented in Hibma et al, 2019

Patients 1, 5, 6: PK after 1st Dose of Maintenance Mylotarg

Pharmacokinetics

	Patient 1 1st Dose	Patient 5 1st Dose	Patient 6 1st Dose	Relapsed/Refractory AML Population (GO Phase 1 Study 0903A1-101-US)[1]					
Parameter	0.5 mg/m²	0.5 mg/m²	0.5 mg/m²	0.25 mg/m²	0.5 mg/m²	1 mg/m²	2 mg/m²	4 mg/m²	5 mg/m²
C_{max} (ng/mL)	**259**	**75**	**374**	15	28	**50**	**411**	611	1,325
AUC_{inf} (Hr*ng/mL)	**26,950**	**4,038**	**1,682**	82	468	**943**	**11,110**	**10,970**	**29,980**

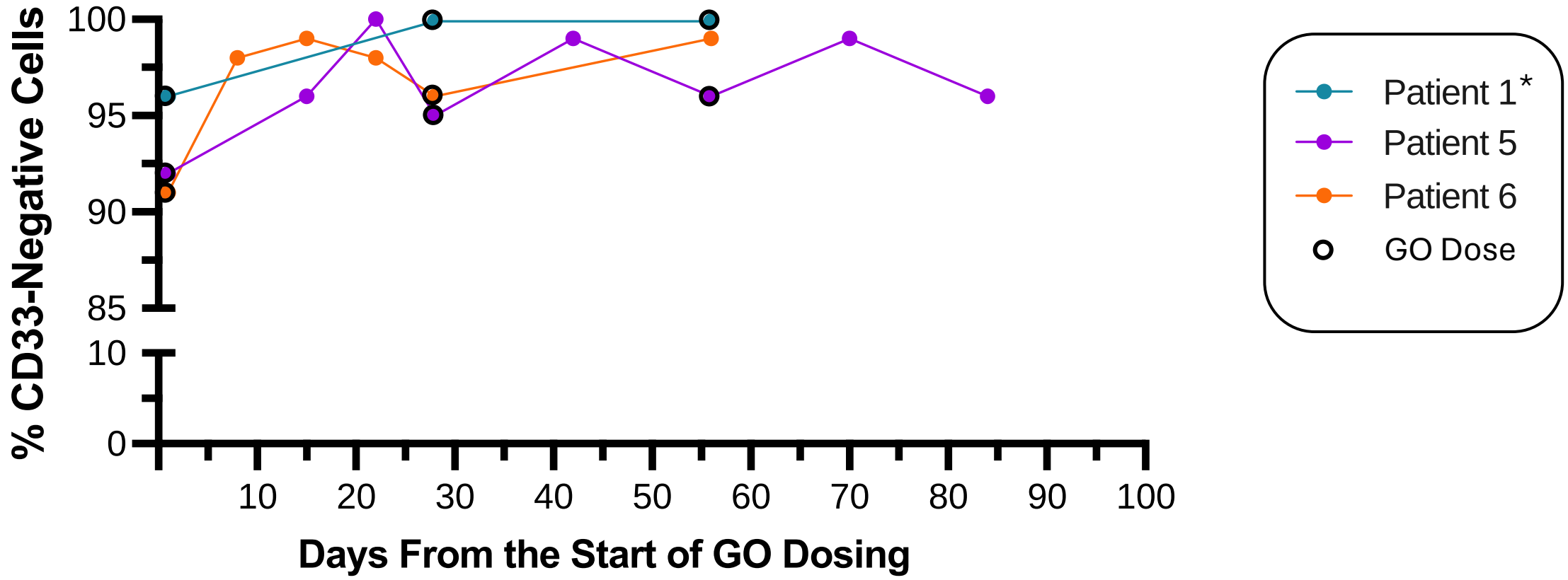
Relationship Between Mylotarg C_{max} and Veno-occlusive Disease in Prior Transplant[1]



[1]Mylotarg ODAC 2017

Increase in CD33 Negative Myeloid Cells during GO dosing

- Editing of CD33 persists over time
- Treatment with GO selects for CD33 negative cells



*Patient 1 CD33 flow contaminated by presence of relapsed disease after 3rd GO dose.

Safety Events Reported as Possibly Related to Either Trem-cel or GO (AE ≥ Grade 3 or any Grade SAE)

Adverse Event	Max Grade	Related to Trem-cel (# of events)	Related to GO (# of events)	SAE (# of events)
Anemia	3	1	—	—
Neutropenia	3	1	—	—
Thrombocytopenia	3	2	—	—
Graft Failure	4	1	—	1
Platelet count decreased	3	—	1	—
Platelet count decreased, worsening	3	1	1	—
Worsening maculopapular rash of whole body	2	1	—	1

For GO dosing:

- No dose-limiting toxicity criteria met
- No increase in liver function tests above upper limit of normal
- No observed SOS/VOD
- Dose Escalation Committee has met and recommended increasing to 1 mg/m^2 dose

Conclusions

- Patients (n=7) transplanted with trem-cel demonstrated primary neutrophil engraftment (Days 8-11), similar to patients who received non-edited CD34 selected grafts.
- Data consistent with CD33 being dispensable for engraftment and hematopoiesis
- Pharmacokinetics showed a higher GO exposure in context of CD33-negative hematopoiesis
- Increase in fraction of CD33-negative cells after GO dosing supports enrichment potentially at the progenitor level.
- GO 0.5 mg/m^2 is well-tolerated after HCT with trem-cel without resulting in deep cytopenias and supporting a protective effect from GO-related myelosuppression
- Potential for heme protection from other CD33-targeted therapies including CART

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Vor Bio

- Clinical
- Manufacturing
- Regulatory/Quality Assurance
- Translational

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