Trem-cel, a CRISPR/Cas9 Gene-Edited Allograft Lacking CD33, Shows Rapid Primary Engraftment with CD33-Negative Hematopoiesis in Patients with High-Risk Acute Myeloid Leukemia (AML) and Avoids Hematopoietic Toxicity During Gemtuzumab Ozogamicin (GO) Maintenance Post-Hematopoietic Cell Transplant (HCT).

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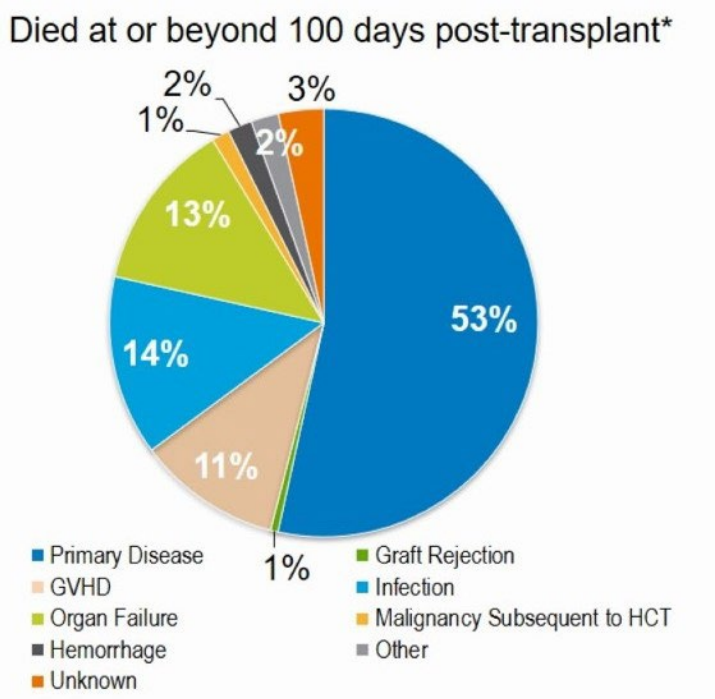
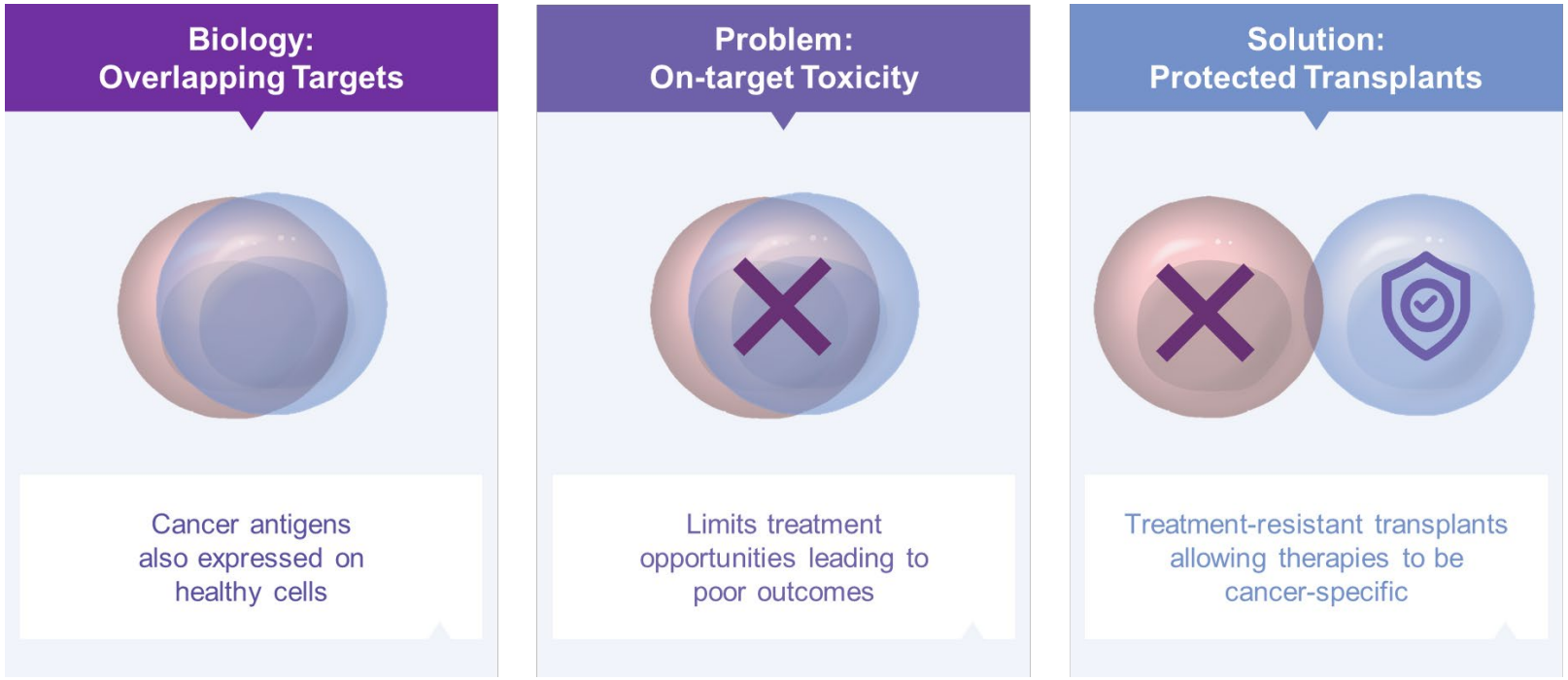
Enabling targeted therapies to reduce risk of relapse without hematotoxicity

Relapse is the leading cause of death post-alloHCT



Adult unrelated donor HCT, CIBMTR 2020



CD33 as a Therapeutic Target

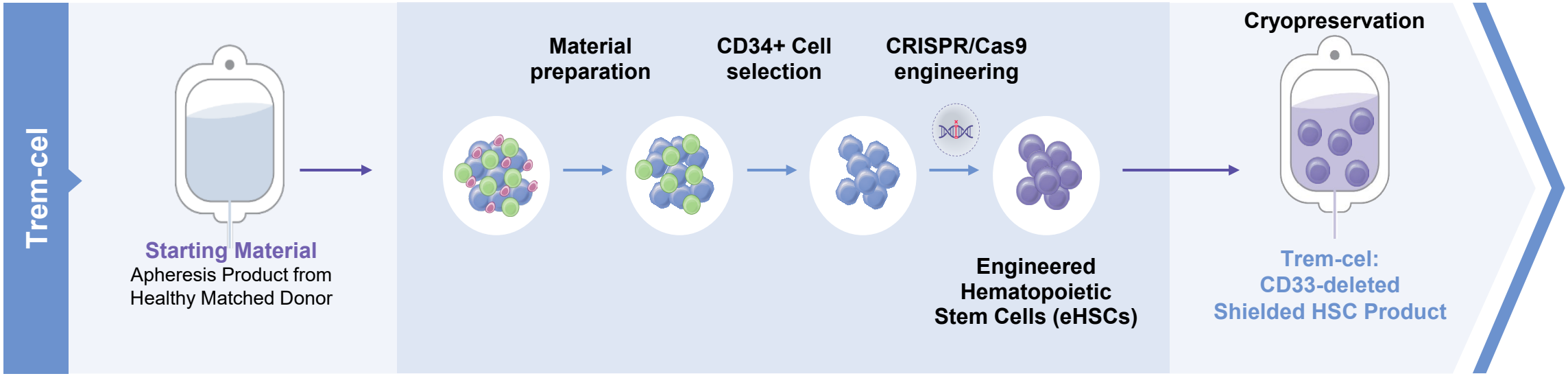
CD33 expression is dispensable

- 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)

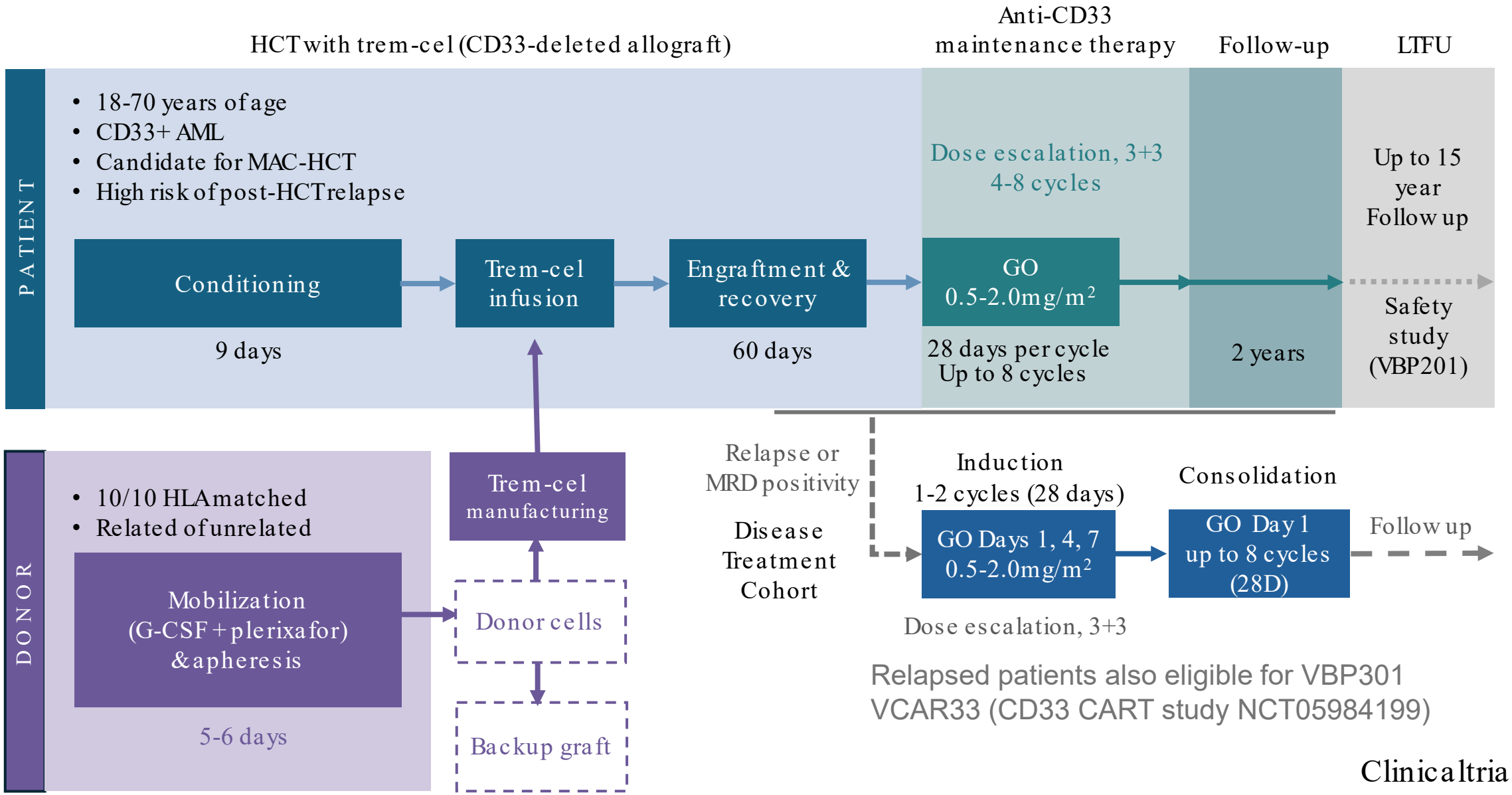
Targeting CD33 in AML

- 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 & RP2D of GO
- RFS, OS, CI of relapse

Patient and trem-cel graft characteristics

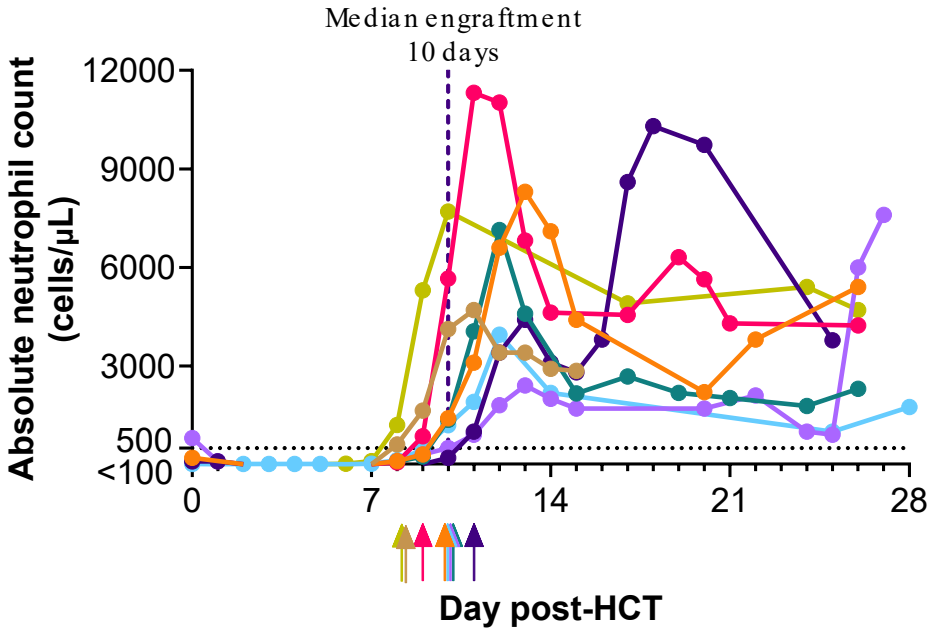
Pt	Age/ Sex	AML & Risk Factors	Weight	10/10 Donor	Dose ($\times 10^6$ CD34 cells/kg)	CD33 Gene Editing
1	64/F	AML with MDS related changes highly complex (adverse) cytogenetics, CR2, Mutant TP53 MRD: 1.8%	69.9 kg	Unrelated	7.6	88%
2	32/M	AML persistent myeloid sarcoma Inv 16 and +22; t(3;3)	120.7 kg	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%
8	57/M	AML (myelomonocytic) with nml karyotype CR2 (CRi/CRp)	68.9 kg	Unrelated	9.5	91%

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: 4 Dec 2023. Presented data from EDC and site/PI communication; pending full source verification

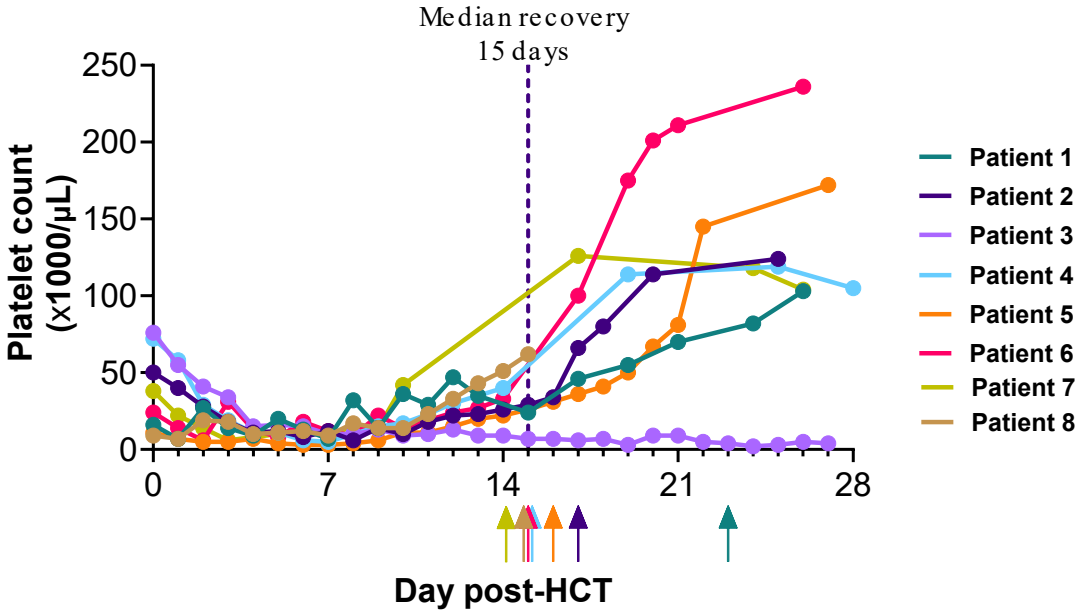
Neutrophil engraftment and platelet recovery are similar to unedited CD34-selected grafts*

Neutrophil Engraftment



Arrows indicate days of individual patient engraftment

Platelet Recovery

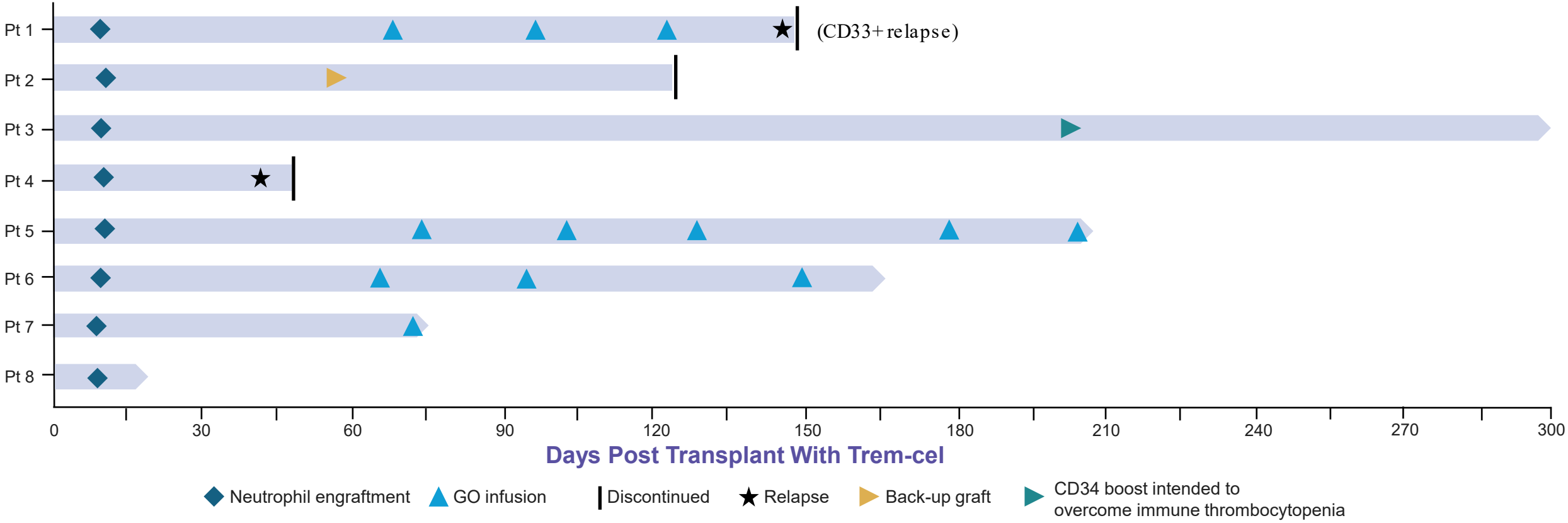


Median excluding pt 3 with immune thrombocytopenia

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 1-8)



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.

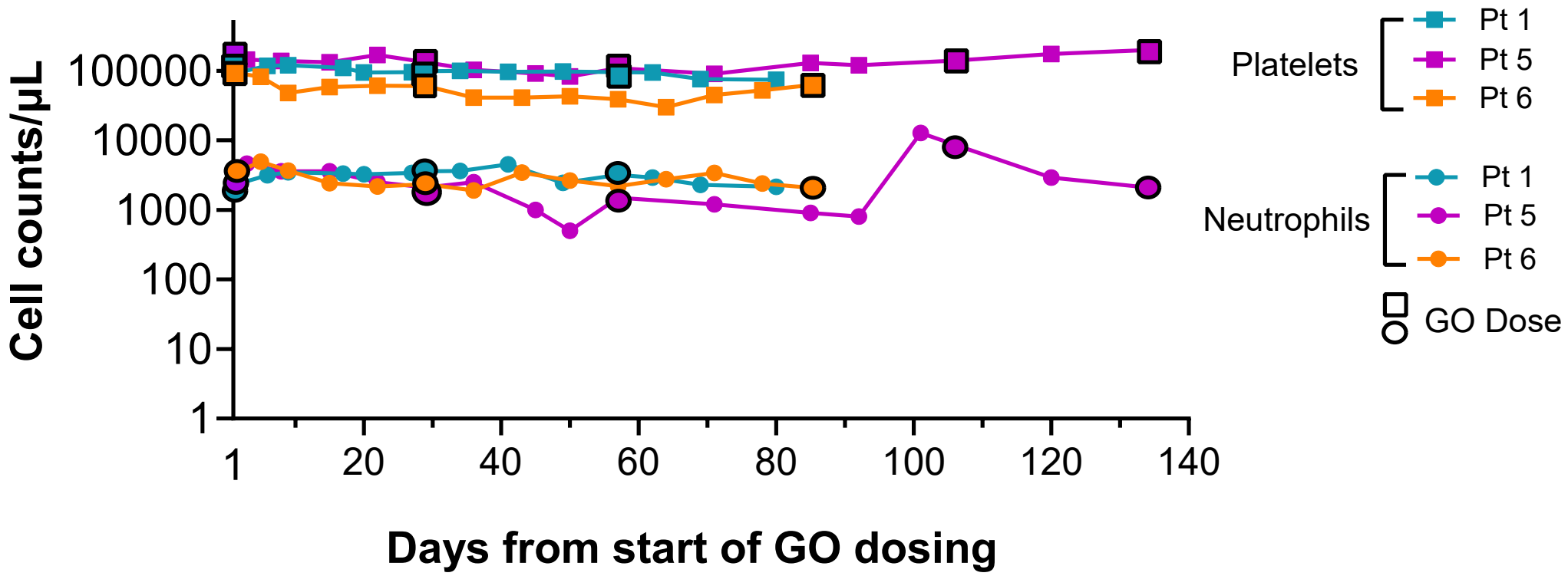
Patient 3

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)



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

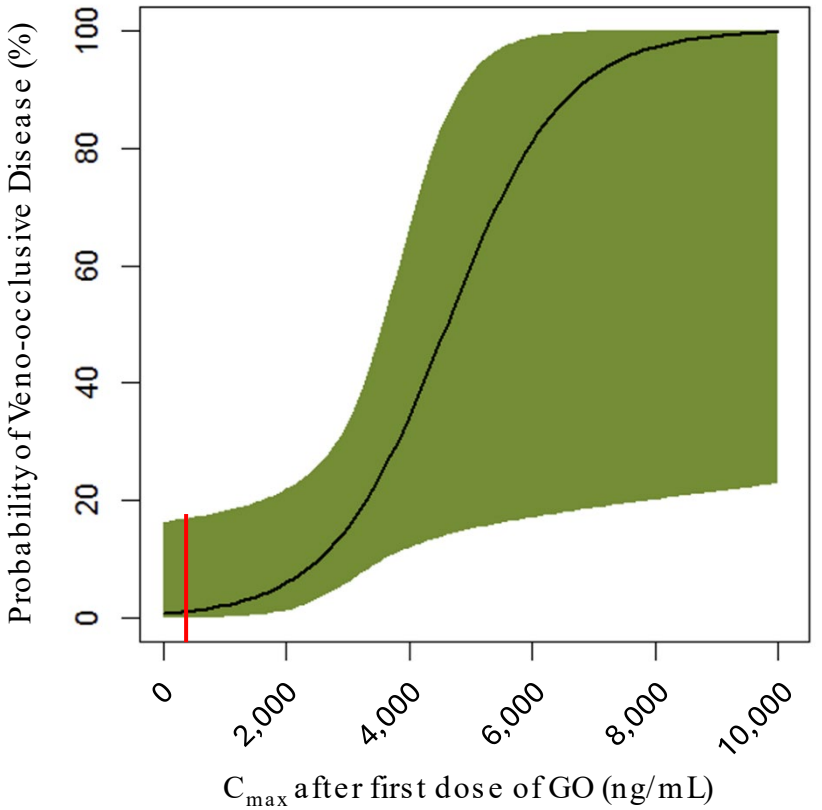
Patients 1, 5, 6: PK after 1st Dose of Maintenance GO

Pharmacokinetics

	VBP101	Relapsed/Refractory AML Population (GO Phase 1 Study 0903A1-101-US)[1]					
Parameter	Mean +/- SD 0.5 mg/m^2	0.25 mg/m^2	0.5 mg/m^2	1 mg/m^2	2 mg/m^2	4 mg/m^2	5 mg/m^2
C_{max} (ng/mL)	236 (+/- 151)	15	28	50	411	611	1,325
AUC_{inf} (Hr*ng/mL)	10,890 (+/- 13958)	82	468	943	11,110	10,970	29,980

Safety (hepatotoxicity) associated with C_{max}
Efficacy vs. disease associated with AUC

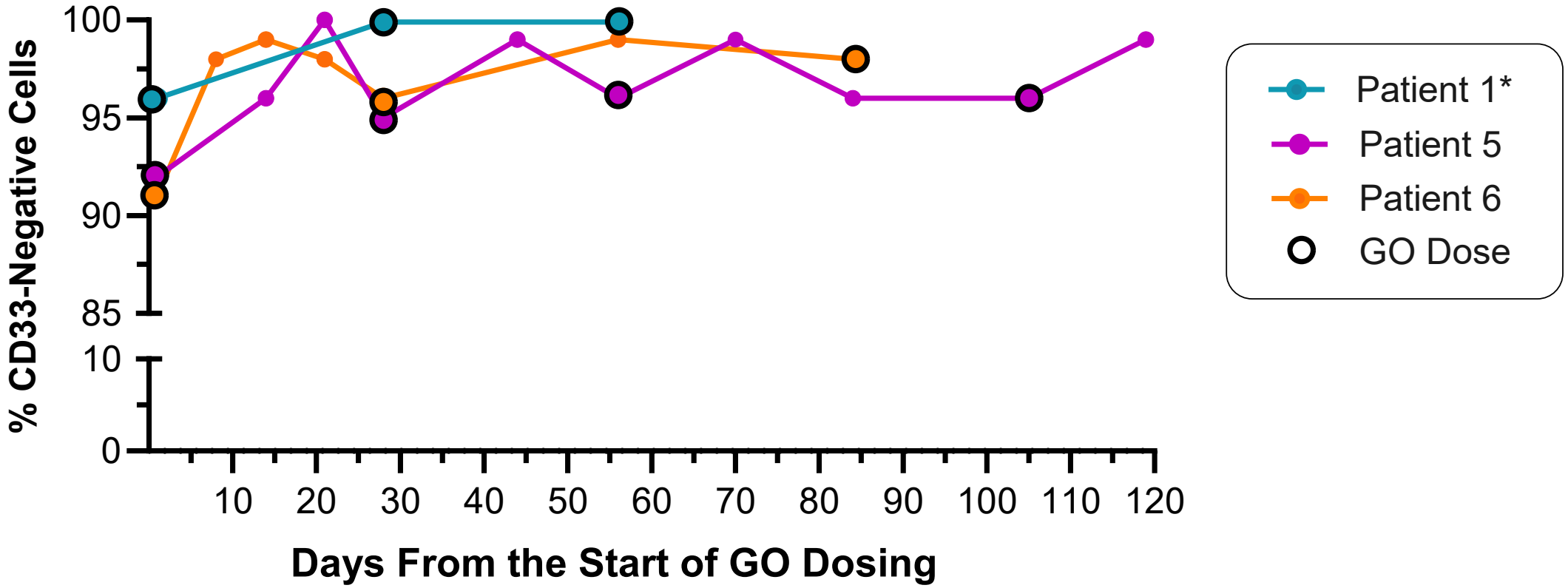
Relationship Between GO C_{max} and Veno-occlusive Disease in Prior Transplant[1]



[1]Mylotarg ODAC 2017

Trending 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 CD33+ relapsed disease after 3rd GO dose.

Conclusions

- All patients (n=8) 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
- Modest increase in fraction of CD33-negative peripheral blood cells after GO dosing suggests enrichment potentially at the progenitor level
- GO 0.5 mg/m^2 is well-tolerated after HCT with trem-cel and blood counts support hematologic protection from known GO-related myelosuppression. GO maintenance dose 1 mg/m^2 now being tested.
- Platform suggests potential for hematologic protection from other CD33-targeted therapies such as CD33 CART

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Vor Bio

- Clinical
- Manufacturing
- Regulatory/Quality Assurance
- Translational

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