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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Background & Methods

Relapse is the leading cause of death for patients undergoing allogeneic HCT for acute myeloid leukemia (AML)[1], particularly for patients with high-risk features such as minimal residual disease (MRD) or adverse cytogenics[2,3]. CD33 is an antigen found on 85-90% of AML cells[4]; however, it is also present on normal myeloid cells[5]. Antineoplastic agents targeting CD33, such as Mylotarg™ (GO), an anti-CD33 antibody-drug conjugate, therefore are associated with extensive cytopenias[6,7]. Preclinical studies have previously shown that CD33 is dispensable for normal biology of human hematopoietic stem and progenitor cells[8]. In order to reduce AML relapse post-HCT, a CRISPR/Cas9 gene-edited, *CD33*-deleted donor allograft, trem-cel (formerly known as VOR33), was developed to enable post-HCT CD33-directed therapies while protecting healthy donor cells from on-target myelosuppression.

VBP101 (NCT 04849910) is a first-in-human (FIH) study, where CD33-positive AML patients at high risk of relapse, such as AML with myelodysplasia (MDS)-related changes (AML-MRC), evidence of persistent bone marrow (BM) blasts, and/or adverse genetic features, undergo myeloablative HCT with trem-cel followed by treatment with low-dose GO. The objective of this study is to evaluate the safety of trem-cel and GO in AML patients at high risk of relapse.

VBP101 Study Design

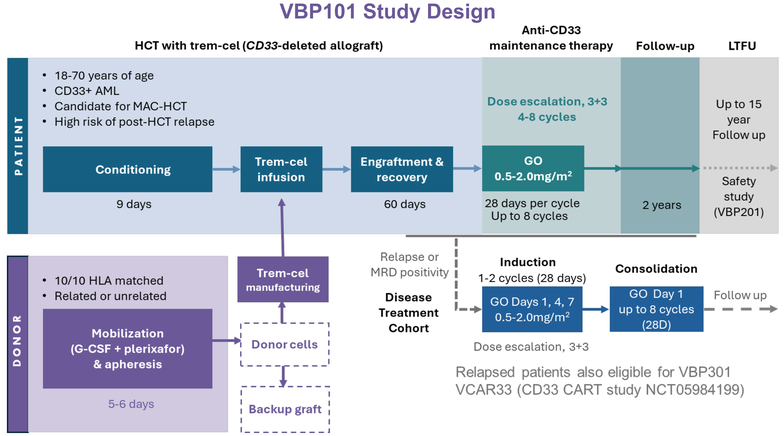

Figure 1: VBP101 Study Design. Dose escalation of GO to determine MTD and RP2D of Maintenance and Disease Treatment arms are independently escalated using a 3+3 strategy.

Patient and Graft Characteristics

Pt	Age/ Sex	AML & Risk Factors	Weight	10/10 Donor	Dose (×10⁶ 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%

Table 1: All patients received myeloablative conditioning with busulfan/melphalan/fludarabine/rabbit anti-thymocyte globulin (ATG), with exception for patient #3, who received equine ATG.

Results

Patient Clinical Courses

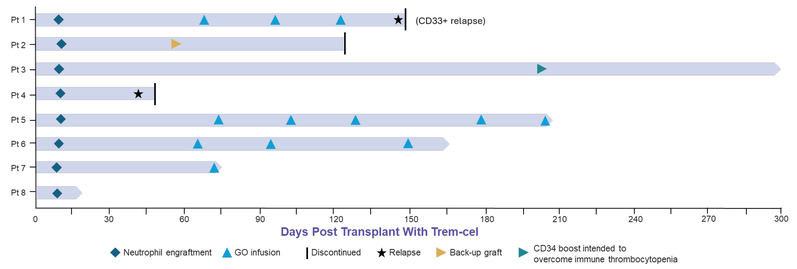

Figure 2: Patient clinical timelines for 8 subjects who received trem-cel. At datacut, four patients received maintenance GO. Three patients (Patients 2, 3, and 4) were ineligible for GO maintenance therapy: Patient 2 had a secondary graft failure in context of prior sepsis, TMP-SMZ/possible DRESS and persistent hKU1 coronavirus infection. Graft failure was resolved after back-up graft given. Patient 3 had immune thrombocytopenia, resolving after treatment with IVIg, steroids, rituximab and CD34 boost. Patient 4 had CNS and systemic relapse prior to GO dosing.

Neutrophil Engraftment and Platelet Recovery Post-HCT with Trem-cel are similar to unedited CD34-selected grafts[9]

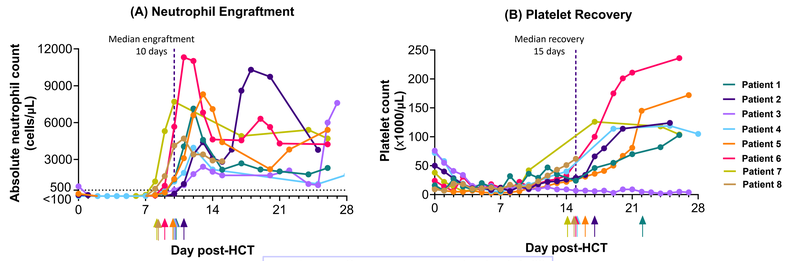

Figure 3: Kinetics of neutrophil engraftment and platelet recovery post-trem-cel HCT **(A)** Absolute neutrophil counts over time post-HCT. Median engraftment day D+10 (range 8-11). Neutrophil engraftment is defined as the first of three consecutive days of an absolute neutrophil count (ANC) ≥500 (dotted line). **(B)** Platelet counts over time post-HCT. Median platelet recovery at D+15 (range 14-22) excluding patient 3 who was treated for immune thrombocytopenia. Platelet recovery defined as the first day of platelet count >20,000/µL (dotted line) with no platelet transfusion in the preceding 7 days. Median neutrophil engraftment and platelet recovery 11 and 17 days respectively for unedited CD34-selected grafts[9] . Arrows under the x-axis indicate day of engraftment/recovery for each patient.

Conclusions

- All patients (n=8) transplanted with trem-cel demonstrated primary neutrophil engraftment (Days 8-11), at a similar median time 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/m² is well-tolerated after HCT with trem-cel and blood counts support hematologic protection from known GO-related myelosuppression. GO maintenance dose 1 mg/m² now being tested.
- Platform suggests potential for hematologic protection from other CD33-targeted therapies such as CD33 CART

Hematologic Protection During Maintenance GO Post-Trem-cel

Cohort 1 (0.5 mg/m²): Neutrophil and Platelet Counts after GO dosing

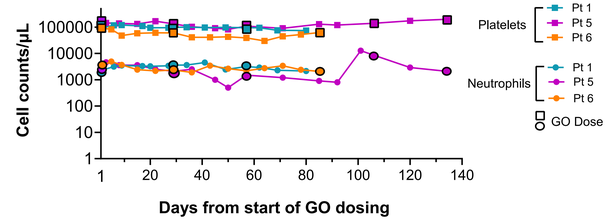

Figure 4: Absolute neutrophil (bottom lines) and platelet counts (top lines) per µL of peripheral blood from start of maintenance GO dosing (0.5 mg/m²) for patients 1, 5 and 6. Repeat GO doses marked by outlined symbols. No dose-limiting toxicity criteria were met. No hepatoxicity was observed as measured by liver function tests and no sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD). The next cohort is currently being dosed at 1 mg/m².

Cohort 1 (0.5 mg/m²): Pharmacokinetics after 1st Dose of Maintenance GO in CD33 negative environment

Parameter	VBP101 Mean +/- SD 0.5 mg/m²	Relapsed/Refractory AML Population (GO Phase 1 Study 0903A1-101-US)[10] 0.25 mg/m²	0.5 mg/m²	1 mg/m²	2 mg/m²	4 mg/m²	5 mg/m²
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

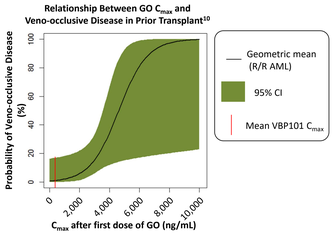

Figure 5: Pharmacokinetics after 1st dose of maintenance GO at 0.5mg/m² for patients 1, 5 and 6. (Left) Mean C_{max} and AUC_{inf} +/- standard deviation (SD) in VBP101 patients compared to PK analyses in a R/R AML population. (Right) Modeled risk of SOS/VOD after GO dosing based on C_{max} (Mylotarg ODAC 2017). The AUC_{inf} for GO at 0.5mg/m² in trem-cel patients are within range of approved doses of GO in R/R AML (1-5 mg/m²). The C_{max} in trem-cel patients (red line) is below 2000 ng/ml inflection point where risk of SOS/VOD increases.

Trending Increase in CD33 Negative Myeloid Cells During GO Dosing

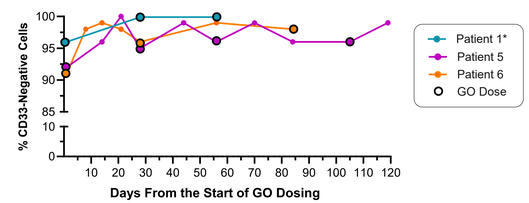

Figure 6: Percentage of CD33 negative myeloid cells in peripheral blood after start of GO dosing for Cohort 1 (0.5 mg/m²). CD33 levels measured by flow cytometry. Outlined circles represent timing of GO dosing. *Note: Patient 1 CD33 flow contaminated by presence of CD33+ relapsed disease after 3rd GO dose.

References

[1]Tsirigotis P. et al. Bone Marrow Transplant 2016;51(11):1431–1438; [2]Norkin M. et al. Blood Cancer J 2017;7(12):634; [3]Hourigan CS. et al. J Clin Oncol 2020;38(12):1273–1283; [4]Ehninger A. et. al. Blood Cancer J 2014;4(6):e218, [5]Kenderian SS. et al. Leukemia 2015;29(8):1637–1647; [6]Stein EM. et al. Blood 2018;131(4):387–396; [7]Walter RB. et al. Expert Opin Investig Drugs 2018;27(4):339–348; [8]Borot F. et al. PNAS 2019;116(24):11978–11987; [9]Luznik L. et al. J Clin Oncol 2022;40(4):356–368; [10]Mylotarg ODAC 2017.

Data compiled from EDC, Lab Reports and PI/site reports, Pending full source data verification. Data cutoff 4 Dec 2023.