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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Background & Methods

Relapse is the leading cause of death for patients undergoing allogeneic HCT for AML. Strategies to reduce relapse including leukemia-directed maintenance therapies post-HCT have been largely ineffective. GO (Mylotarg™) is an anti-CD33 antibody-drug conjugate approved for use in AML, but its use has been limited by hepatotoxicity and on-target, off-tumor hematopoietic toxicity toward CD33+ normal blood cells leading to severe cytopenias, especially post-HCT. Tremtelectogene empogeditemcel (trem-cel; formerly VOR33) is a hematopoietic stem and progenitor cell product manufactured from CD34+ cells from a matched donor and CRISPR/Cas9 gene-edited to delete CD33. Trem-cel was developed to shield normal hematopoietic cells from CD33-directed therapies and allow exclusive targeting of residual CD33+ leukemia.

VBP101 (NCT04849910) is a Phase 1/2 multicenter trial to establish the safety of using trem-cel as an allograft followed by GO maintenance therapy for patients with CD33+ AML or MDS who are at high risk of relapse and undergoing HCT. Patients (18-70 y) must have CD33+ AML/MDS with high-risk features for relapse, such as adverse-risk cytogenetics or measurable residual disease, and an 8/8 HLA-matched related or unrelated donor. Trem-cel is manufactured from donor CD34+ cells isolated from G-CSF/Plerixafor-mobilized peripheral blood. Patients undergo busulfan- or TBI-based myeloablative conditioning with rATG prior to HCT with trem-cel. After ~60 days post-HCT patients begin maintenance therapy with GO in a 3+3 dose escalation strategy with cohorts of 0.5, 1 and 2 mg/m2. GO is dosed at a planned 28 days between cycles for 4-8 cycles. Relapsed patients could receive subsequent therapies including VCAR33 (a donor-derived CD33 CAR-T, NCT05984199).

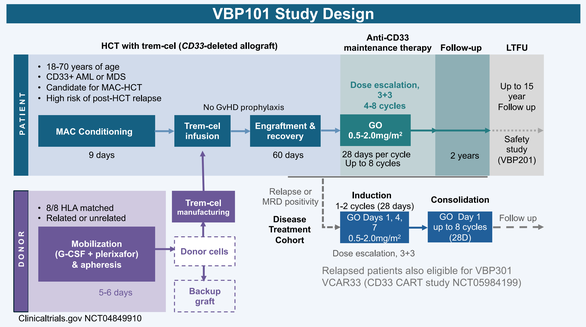

Figure 1: VBP101 Study Design. Dose escalation of GO to determine MTD and RP2D of Maintenance and Disease Treatment arms are independently escalated using a 3+3 strategy.

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Patient Demographics, Graft Characteristics, Disease Characteristics, and Baseline Risk Factors

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 (x10⁶ 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%)
Disease Burden Status | N=25	
Remission (MRD neg)	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%)

[b] Defined as AML-MRC: AML with myelodysplasia-related change (9/24) or therapy-related (1/24)

Values are median (range) or n (%)

Table 1. Patient Demographics, Graft Characteristics, Disease Characteristics, and Baseline Factors

References

[1]Luznik L. et al. J Clin Oncol 2022, 40 (4); [2]Mylotarg ODAC 2017; [3]Jentzsch M. et al. Blood Cancer J 2022; 12 (170); [4]Araki D. et al. J Clin Oncol 2016, 34(4) [5]Goldberg et al Leuk and Lymph 58 (217); [6]Llaurador et al. Transplantation and Cellular Therapy 27 (2021); [7]O'Reilly et al Biol Blood Marrow Transplant 26 (2020)

Data compiled from EDC, Lab Reports and PI/site reports, Pending full source data verification. Data cutoff 01Nov2024.

Results

Patient Clinical Courses

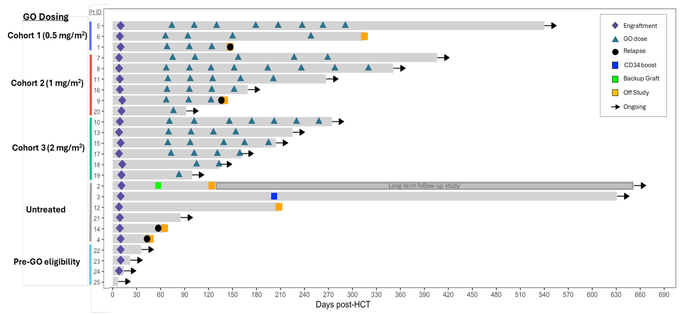


Figure 2. Patient clinical course swimplot.
Disposition of patients not treated with GO: Pt 2: Secondary graft failure in context of ongoing seasonal coronavirus infection. Recovered after receiving Backup graft; Pt 3: Delayed platelet recovery with anti-platelet antibody. Received unedited CD34 boost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

Neutrophil Engraftment and Platelet Recovery Post-HCT with Trem-cel are Similar to Unedited CD34-selected Grafts[1]

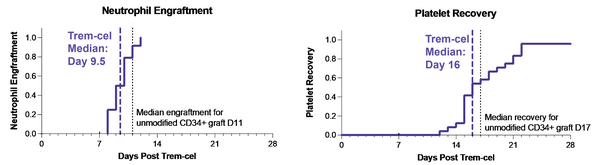
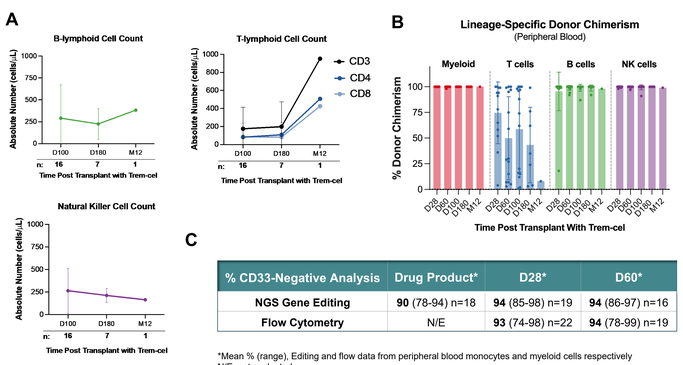


Figure 3. Neutrophil engraftment (L) and platelet recovery (R). Neutrophil engraftment is defined as the first of three consecutive days of an absolute neutrophil count (ANC) ≥500. Platelet recover defined as the first day of a sustained platelet count ≥20,000/µL with no platelet transfusion in the preceding seven days. At time of data cut, one patient had yet to achieve neutrophil engraftment and platelet recovery. Median neutrophil recovery and platelet recovery for trem-cel was D+9.5 (range 8-12) at D+16 (range 12-22), respectively. Median platelet recovery excludes patient 3 who was treated for immune thrombocytopenia.

Immune Reconstitution, Full & Sustained Myeloid Chimerism, and CD33-Negative Myeloid Compartment Are Observed



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

Figure 4. (A) Immune Reconstitution (B) Multi-lineage Donor Chimerism (C) CD33-negative myeloid reconstitution via NGS gene editing and flow cytometry at days 28 and 60 post-HCT.

Maintenance Dosing of Gemtuzumab Ozogamicin (GO) post-Trem-cel HCT

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

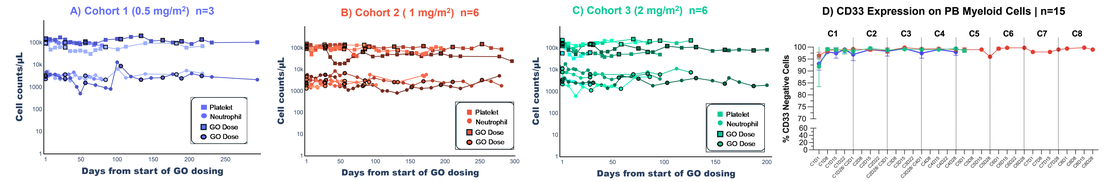
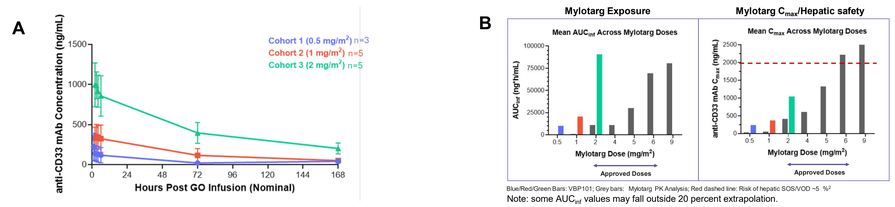


Figure 5. Neutrophil and platelet count of subjects treated in (A) Cohort 1 (0.5 mg/m²), (B) Cohort 2 (1.0 mg/m²) and (A) Cohort 3 (2 mg/m²). (D) CD33 expression on peripheral blood myeloid cells by flow cytometry upon GO dosing.

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



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

Figure 6. (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).

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

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%)	-
Hepatobilary					
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

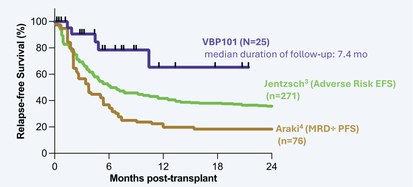
Table 2. Patient adverse events (highest grade) after GO dosing in patients receiving GO (n=15)

Note: Review of the first 6 patients receiving 2mg/m² by the Dose Escalation Committee (DEC) on 22 Nov 2024 determined the 2 mg/m2 dose was safely tolerated and is the Recommended Phase 2 Dose (RP2D) for subsequent patients

Trem-cel Relapse-Free Survival

Study	Median RFS (mo)	P value vs. VBP101	Hazard Ratio* (HR)	HR 95% CI*
VBP101	Not reached			
Jentzsch	6.2	0.02	0.36	0.21 – 0.64
Araki	3.8	0.0004	0.23	0.14 – 0.40

* 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

Figure 7. Relapse-Free Survival of VBP101 patients compared to published adverse risk genetics or MRD+ populations

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/m2 GO doses. Dose Escalation Committee confirmed 2 mg/m2 as Recommended Phase 2 Dose.
- ❑ Immune reconstitution and multilineage chimerism consistent with unedited CD34-selected grafts.[5-7]
- ❑ Broadened therapeutic index for GO following trem-cel as demonstrated by increased AUC, correlated with efficacy, and proportionally lower increase in C_{max}, 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.