Phase 1/2 Study of Donor-Derived Anti-CD33 Chimeric Antigen Receptor Expressing T Cells (VCAR33^{ALLO}) in Patients with Relapsed or Refractory Acute Myeloid Leukemia After Allogeneic Hematopoietic Cell Transplantation (Trial in Progress)

#4862

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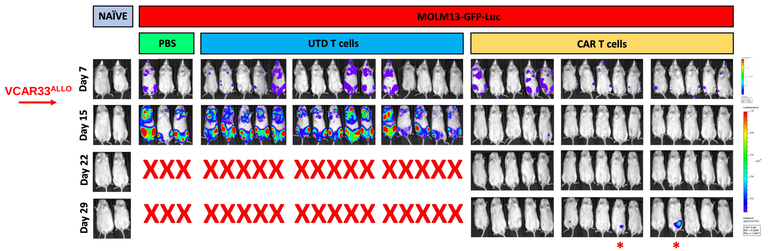
Background And Significance

- Though allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative therapy for patients with high-risk acute myeloid leukemia (AML), post-HCT relapse occurs in up to 70% of these patients[1]
- Clinical experience with chimeric antigen receptor (CAR) T cell therapies for AML is limited
- Challenges for autologous AML CAR T cell therapy include:
- Difficulty harvesting adequate numbers of functional, undifferentiated T cells as CAR T cell starting material
- T cells from post-alloHCT patients may be exposed to immunosuppression, which can further reduce activity
- Presence of AML blasts in an autologous cell collection may interfere with T cell proliferation and function during the manufacturing process
- CD33 is expressed on the majority (>80%) of AML blasts and is an established target for AML therapy
- VCAR33^{ALLO} is a CD33-directed CAR T cell product generated from lymphocytes from each patient's prior matched allogeneic stem cell donor
- CAR T cell manufacture from HLA-matched donors can eliminate delays and failures in production due to lymphopenia and may also improve CAR T cell function by using healthy starting material

VCAR33^{ALLO}

- Allogeneic CD4+ and CD8+ T cells transduced with a replication defective lentiviral vector expressing a CAR that targets CD33[2]
- Lintuzumab scFv (Hu195; SGN-33): binding domain derived from unconjugated humanized murine monoclonal antibody against CD33
- CD28 and CD3ζ internal costimulatory domain
- Same CAR construct used for manufacturing autologous CD33CART in a Phase 1/2 study (NCT03971799)
- ASH abstract 771, "CD33 CAR T-cells (CD33CART) for Children and Young Adults with Relapsed/Refractory AML: Dose-Escalation Results from a Phase I Multicenter Trial", Oral Presentation, Monday, December 11, 2023, 11:00 AM

In vivo Efficacy Of VCAR33^{ALLO} In A Murine Tumor Model



Representative total body bioluminescence images of NSG mice injected with MOLM13-GFP-Luc cells and treated with PBS, VCAR33^{ALLO} or UTD T Cells. Images were taken weekly starting 1 week after the inoculation of AML cells. Red crosses (x) represent animals euthanized or found dead during the study.

(Courtesy of Dr. Giacomo Canesin, Vor Biopharma)

Study Design

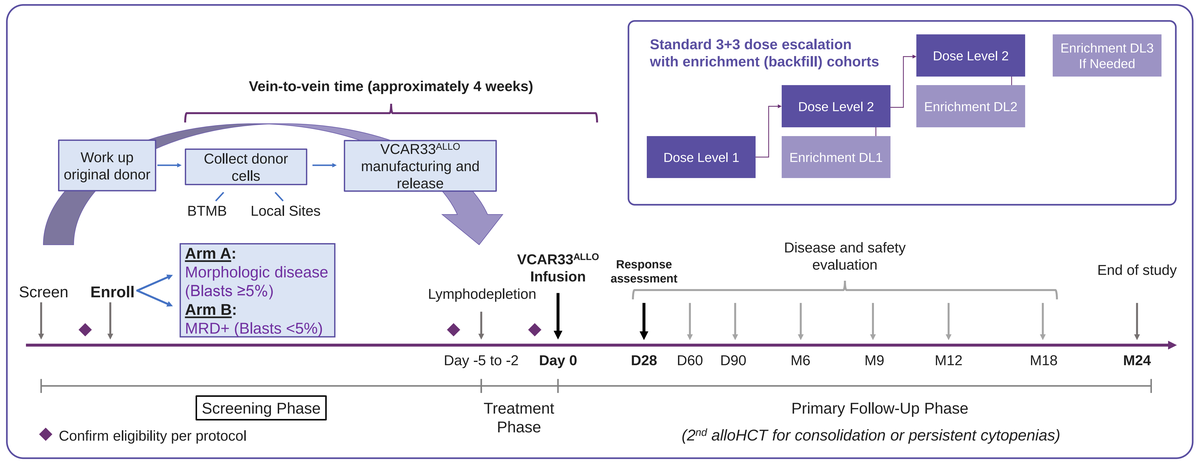
- VBP301 is an open-label, multicenter, phase 1/2 study (NCT05984199)
- Patients with relapsed/refractory (R/R) AML after alloHCT will be enrolled into 2 arms based on disease burden (Arm A: Morphologic disease and Arm B: MRD positive)
- VCAR33^{ALLO} will be manufactured from each patient's original matched stem cell donor and given as a one-time infusion
- The maximum tolerated dose (MTD) of VCAR33^{ALLO} will be determined using a 3+3 trial design within each arm
- Three planned dose levels, starting with Dose Level 1: 1 x 10^6 CAR T cells/kg
- Total projected enrollment: 24-36 patients (12-18 per arm), with up to 40 additional patients into enrichment cohorts

Key Inclusion Criteria

- Age ≥18 years
- CD33+ AML in relapse after 1st alloHCT
  - Recipient of 8/8 HLA-matched related or unrelated donor alloHCT
  - Patients with R/R AML after trem-cel HCT (NCT04849910) may also be considered
- Disease status:
  - Arm A: Morphologic disease (≥5% blasts in BM)
  - Arm B: MRD positive (<5% blasts in BM with at least 0.1% CD33+ AML by flow cytometry)
- Original donor eligible and willing to undergo non-mobilized apheresis
- Donor options for 2nd alloHCT have been identified

Key Exclusion Criteria

- Greater than 1 prior alloHCT
- <100 days post prior alloHCT at the time of VCAR33^{ALLO} infusion
- H/o Grade III-IV acute GVHD or severe chronic GVHD
- Active GVHD requiring systemic immunosuppression
- Disease status:
  - Active CNS involvement with AML
  - Hyperleukocytosis (≥30,000 blasts/μL) or rapidly progressive disease
- DLI within 28 days of enrollment
- Prior CAR T therapy



Patient

- Patient consent & eligibility determination
- Bridging chemotherapy (Investigator choice*)
- Disease reassessment (2 weeks prior to start of lymphodepletion)
- Lymphodepletion (Outpatient or Inpatient)
- VCAR33^{ALLO} infusion (Inpatient)

Original HCT Donor

- Medical clearance by local site (related) or NMDP (unrelated)
- Apheresis (not started until patient deemed eligible)
- VCAR33^{ALLO} manufacture and release

*Bridging therapy may be administered up to 14 days prior to start of LD, except for hydroxyurea and low dose agents which may be administered until LD.

Eligibility Criteria Prior to LD Start

- VCAR33^{ALLO} must have met release criteria
- Disease evaluation (bone marrow aspirate/biopsy) performed within 2 weeks of LD start to confirm arm assignment
- ECOG 0 or 1
- Adequate cardiopulmonary status without need for vasoactive or supplemental oxygen support
- No signs of new uncontrolled infection
- No evidence of rapidly progressive AML

Treatment Plan

Day	Lymphodepletion
-5,-4	fludarabine 30 mg/m^2/day
-3,-2	fludarabine 30 mg/m^2/day + cyclophosphamide 500 mg/m^2/day
-1	Rest Day
Day 0: VCAR33^{ALLO} Infusion	

Objectives and Endpoints

	Objectives	Endpoints
Primary	Safety and maximum tolerated dose (MTD) of VCAR33^{ALLO} in patients with R/R AML after alloHCT	• Incidence of dose-limiting toxicities
Secondary	• Evaluate further safety and toxicity of VCAR33^{ALLO} • Determine the efficacy of VCAR33^{ALLO} in patients with R/R AML after alloHCT	• Incidence of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and sinusoidal occlusion syndrome (SOS) related to VCAR33^{ALLO} • Incidence of cytopenias post-VCAR33^{ALLO} infusion • Incidence of acute and chronic graft versus host disease related to VCAR33^{ALLO} • Percentage of patients who achieve response by 2022 ELN criteria for AML • Overall survival and progression-free survival post-VCAR33^{ALLO} infusion • Frequency of patients who proceed to second alloHCT post-VCAR33^{ALLO} infusion

Summary

- VBP301 is an open-label, multicenter, phase 1/2 study of donor-derived anti-CD33 CAR T cells (VCAR33^{ALLO}) in patients with R/R AML after alloHCT with an 8/8 HLA-matched donor, including patients who relapse after a trem-cel transplant
- Patients will be enrolled into a Morphologic disease arm or an MRD positive arm
- Total projected enrollment: 24-36 patients (12-18 per arm), with up to 40 additional patients into enrichment cohorts

(**NCT05984199**)

Abbreviations: BM, bone marrow; BTMB, Be The Match BioTherapies; CNS, central nervous system; DLI, donor lymphocyte infusion; HLA, human leukocyte antigen; LD, lymphodepletion; MRD, measurable residual disease; NSG, NOD-scid IL2Rynull mice; PBS, phosphate buffered saline; R/R, relapsed/refractory; UTD, untransduced

References: [1]Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, Mielcarek M, Estey EH, Appelbaum FR, Walter RB. J Clin Oncol. 2016;34(4):329-336; [2]Qin H, Yang L, Chukinas JA, et al. J Immunother Cancer. 2021 Sep;9(9):e003149.

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