



The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

CD33 CAR T-Cells (CD33CART) for Children and Young Adults with Relapsed/Refractory AML: Dose-Escalation Results from a Phase I/II Multicenter Trial

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Introduction: Current therapies for patients with acute myeloid leukemia (AML) push the limits of chemotherapy intensity but cure only 30% of adults and 70% of children. Recently developed antibody-based therapies and molecularly-targeted agents only modestly improve outcomes for select patient subsets. Thus, new approaches are needed. Given the success of chimeric antigen receptor (CAR) T-cell therapies for acute lymphoblastic leukemia (ALL), we developed and optimized a novel CD33 CAR T-cell (CD33CAR) construct for clinical testing in a multicenter Phase I/II clinical trial in children, adolescents, and young adults (AYA) with relapsed/refractory (r/r) AML. (Qin H, et al. *JITC* 2021) We report interim results following completion of the dose-escalation phase.

Methods: This multicenter phase I/II clinical trial (NCT03971799) was conducted as a 3+3 dose escalation study through the Pediatric Transplantation and Cell Therapy Consortium with National Marrow Donor Program sponsorship and managed by CIBMTR CRO. Autologous CD33CAR product were centrally manufactured on a ClinMACS Prodigy® by the Biopharmaceutical Development Program at the Frederick National Laboratory for Cancer Research (NCI). Eligibility criteria were r/r AML in subjects < 35 years old with adequate organ/performance status and an identified allogeneic stem cell transplant (SCT) donor. Bone marrow assessment was used for standard morphologic evaluation and central flow cytometric minimal residual disease (MRD) quantification. All subjects received pre-CD33CAR lymphodepleting chemotherapy (LD) with fludarabine (75-120 mg/m²) and cyclophosphamide (900-1000 mg/m²). CD33CAR doses levels (DLs) were: DL1: 3 x 10⁵ CD33 CAR+ T-cells/kg; DL2: 1 x 10⁶/kg; DL3: 3 x 10⁶/kg and DL4: 1 x 10⁷/kg. Adverse event grading used CTCAE v5 with incorporation of ASTCT consensus definitions for cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS). Dose-limiting toxicities (DLTs) included > grade 3 CRS, > grade 3 ICANS, and persistent > grade 3 non-hematologic toxicity that did not resolve < grade 2 in 72 hours. CD33CAR persistence was assessed via flow cytometric evaluation of the blood and bone marrow. Data cut-off was June 1, 2023.

Results: A total of 24 subjects (median age of 16 years, range 1-34 years), were enrolled, 12 (50%) of whom underwent a prior SCT. CD33CAR products were successfully manufactured for 23 subjects and infused into 19. In 4 non-infused subjects with manufactured products, 1 died from progressive disease (PD) prior to LD, 2 transitioned to palliative care and 1 withdrew consent to seek alternative therapy. Manufacturing was not performed in one subject due to death from PD after enrollment. One morbidly obese subject (BMI=49.3) enrolled at DL4 but received treatment at DL3 due to weight-based manufacturing limitations.

The median time from enrollment to infusion was 47 days (range, 24-242). (Table) Three subjects each were infused at DL1 and DL2 without DLTs. At DL3, 1 subject experienced DLT (grade 4 CRS) prompting expansion at this dose level, and no subsequent DLTs were observed. At DL4, 1 subject experienced a prolonged grade 3 CRS (> 72 hours) and grade 3 ICANS, both constituting DLT and necessitating expansion of the cohort without additional DLTs seen. Across all dose-levels, CRS was seen in 13 (68%) patients and was > grade 3 in 4 (21%) with onset typically within the first 24 hours post-infusion. Complete remission (CR) was only seen at DL4 and achieved in 2 subjects, both achieving an MRD negative CR alongside myeloid aplasia. One SCT naïve subject developed candidemia during aplasia but was able to proceed to an allogeneic SCT, achieved engraftment, and was in remission at Day +100 post SCT. The second patient (post-two prior SCTs) declined third SCT, had spontaneous count recovery and remained in remission until day +119 (MRD+ relapse). Transient CD33CAR expansion was detected in 9 (47.4%) subjects overall and in all 6 (100%) subjects at DL4.

Conclusions: CD33CAR manufacturing is feasible in children and AYAs with r/r AML with acceptable toxicity experienced in treated subjects. CD33CAR expansion was best in subjects treated at DL4 (1 x 10⁷/kg) with MRD negative CRs and transient myeloid aplasia occurring in 2 of 5 (40%) subjects evaluable for response (Table). Based on early clinical efficacy at DL4, enrollment continues in the phase 2 portion.

Disclosures Shah: VOR: Consultancy, Research Funding; *Immunoadoptive Cell Therapy Private Limited:* Consultancy, Other: Scientific Advisory Board; *CARGO:* Consultancy; *Lentigen:* Research Funding. **Tasian:** Amgen: Other: travel support ; *Kura Oncology:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Beam Therapeutics:* Research Funding; *Aleta Biotherapeutics:* Membership on an entity's Board of Directors or advisory committees; *Incyte Corporation:* Research Funding; *Syndax Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees. **Baumeister:** Takeda: Other: Husband is an employee at Takeda. **Pollard:** Servier: Research Funding; *Abbvie:* Research Funding. **Auletta:** Takeda: Membership on an entity's Board of Directors or advisory committees; *National Marrow Donor Program:* Current Employment; *AscellaHealth:* Membership on an entity's Board of Directors or advisory committees. **Kean:** Gilead: Research Funding; *Merck EMD Serono:* Research Funding; *Novartis:* Research Funding; *Tessera:* Research Funding; *Vertex:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Bristol Myers squibb:* Patents & Royalties: royalties for clinical trial results., Research Funding; *HiFiBio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Mammoth:* Consultancy, Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Vor:* Other: Materials Transfer Agreement; *Regeneron:* Research Funding. **Pulsipher:** *Adaptive:* Research Funding; *Gentibio:* Membership on an entity's Board of Directors or advisory committees; *Miltenyi:* Research Funding; *Vertex:* Membership on an entity's Board of Directors or advisory committees; *BlueBird:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy; *CARGO:* Membership on an entity's Board of

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Table 1. Summary of Infused Subjects, Toxicities, Response and CD33CART Expansion					
	DL1 (3 x 10 ⁵)*	DL2 (1 x 10 ⁶)*	DL3 (3 x 10 ⁶)*	DL4 (1 x 10 ⁷)*	Total
# infused	3	3	7 [@]	6	19
Male, n (%)	0 (0%)	3 (100%)	6 (86%)	4 (67%)	13 (68%)
Age at enrollment, in years, median (range)	22 (19-32)	24 (10-34)	15 (5-30)	10 (1-25)	16 (1-34)
Days from enrollment to infusion, median (range)	47 (34-63)	52 (33-68)	36 (24-242)	46 (33-56)	47 (24-242)
# with Prior HCT, (%)	2 (67%)	2 (67%)	3 (43%)	3 (50%)	10 (53%)
# experiencing DLT, (%)	0 (0%)	0 (0%)	1 (14%)	1 (17%)	2 (11%)
# with any CRS, (%)	1 (33%)	2 (67%)	5 (71%)	5 (83%)	13 (68%)
# with ≥ Grade 3 CRS, (%)	0 (0%)	1 (33%)	2 (29%)	1 (17%)	4 (21%)
# with ICANS, (%)	0 (0%)	0 (0%)	0 (0%)	1 (17%) **	1 (5%)
# with CR, (%)	0 (0%)	0 (0%)	0 (0%)	2 (40%) ^	2 (11%)
# with CART expansion, (%)	1 (33%)	0 (0%)	4 (57%)	6 (100%)	11 (58%)

*Dose is represented as total transduced CD33+ CAR T-cells/patient weight (kg).
[@]An additional patient was enrolled at DL4 but treated at DL3 due to manufacturing limitations based on dosing at their weight.
^{**}ICANS was grade 3 and manifested with decreased responsiveness without any evidence for cerebral edema or seizures and an immune effector cell-associated encephalopathy (ICE) score of 0
[^]Only 5 patients were evaluable for response as one participant was in a minimal residual disease CR at the time of infusion, thus the denominator for patients evaluable for response at DL4 is n=5.

Abbreviations: CART: CAR T-cell; CR: complete remission; CRS: cytokine release syndrome; DL: Dose level; DLT: dose limiting toxicity; HCT: hematopoietic cell transplantation; ICANS: immune effector cell associated neurotoxicity syndrome

Figure 1

<https://doi.org/10.1182/blood-2023-179667>

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