Abstract #7043: An Analysis of a First-In-Human Study of NEXI-001 Donor-Derived Antigen-Specific CD8⁺ T-Cell Treatment of Relapsed AML after Allogeneic Hematopoietic Cell Transplantation (HCT)

Authors: Monzr M. Al Malki[1], Sumithira Vasu[2], Dipenkumar Modi[3], Suzanne Afonso-Smith[4], Sojung Kim[4], Emily Lu[4], Guido Marcucci[1], Mathias Oelke[4], Robert D. Knight[4], and Juan C. Varela[5]

(1)Hematology/Hematopoietic Cell Transplant, City of Hope National Medical Center, Duarte, CA, (2)Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus Ohio, (3)Division of Oncology, Karmanos Cancer Center/Wayne State University, Detroit, MI, (4)NexImmune, Inc., Gaithersburg, MD, (5)Beth Israel Deaconess Medical Center, Dana Farber/Harvard Cancer Center, Boston, MA

Background/Methods:

- Acute myeloid leukemia (AML) is an aggressive malignancy. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) offers the potential for long-term survival for AML patients with intermediate- or adverse-risk AML and for patients with relapsed/refractory AML.
- However, relapse after an allo-HSCT is a difficult clinical challenge. Subsequent remissions are infrequent, and the 2-year survival rate is < 10% to 15%.
- Because the graft versus leukemia (GVL) effect resulting from an allo-HSCT is mediated by donor T lymphocytes, activated T-cell-directed therapy that enhances the GVL effect may represent an effective post-allo-HSCT relapse treatment.

Methods:

- We report the results of a Phase 1 dose-finding study utilizing a 3+3 dose-escalation design in AML patients who had relapsed after an allo-HCT from matched HLA donors, and refractory to salvage therapy in 3 dosing cohorts.
- NEXI-001 T cells are a non-genetically engineered adoptive cellular therapy (ACT) consisting of donor-derived CD8⁺ T cells targeting 5 HLA A2-restricted peptides from WT1, PRAME, and Cyclin A1 that are commonly expressed on AML blasts.
- NEXI cellular products include early T-cell memory subtypes, which have been associated with anti-leukemia efficacy and long-term persistence.
- Persistence of antigen-specific T cells in peripheral blood and bone marrow was determined using flow cytometry by multimer-based staining.

Results – Demographics & Baseline Characteristics:

Cohort (Planned Cycles)	Dose (Actual Cycles)	Pt #	Age Gender/ Donor	Prior Response to Induction Rx	SCT to relapse (month)	Prior GvHD	Adverse Cytogenetic/Mutations	Extramedullary Disease? Yes/No
Cohort 1 (1 cycle)	50M T cells on D1 (1 cycle)	1285 -001	65 M/MUD	Refractory	5	Hx GvHD skin; on steroid inhaler	RUNX1/ ASXL1	Yes, CNS disease
	100 M T cells on D1 (1 cycle)	1091 -003	40 M/MRD	Refractory	78	Hx GvHD of eye, mouth	No abnormal blasts	Yes, retroperitoneal masses
		1091 -004	72 F/MUD	Refractory	3	Unknown	FLT3-ITD	No
		1091 -006	43 M/MUD	Refractory	10	Hx GvHD of skin, mouth, eyes, GI & joints	P53 and complex karyotype	No
Cohort 2 (allowed > 1 cycle)	200M T cells on D1 (2 cycles)	1091 -005	23 M/MUD	Refractory	25	Hx GvHD skin	Monosomy 7	No
		1285 -005	68 M/MUD	Responded	4	Hx GvHD (type UNK)	RUNX1/ ASXL1	No
	200M T cells on D1 (1 cycle)	1091 -018	46 M/MUD	Refractory	3	Hx GvHD skin & liver on steroids	GATA2	No
		1091 -017	55 F/MUD	Responded	24	Hx of GvHD skin, mouth, eyes, liver	RUNX1	No
Cohort 3 (allowed > 1 cycle)	200M T cells on D1, D8 & D15 (1 cycle)	1243 -004	46 F/MRD	Refractory	9	Hx of GVHD of skin, liver, GI Steroids (prior/during)	DNMT3A	No
		1091 -026	76 F/MUD	Responded	19	Hx of GVHD of eyes, mouth Steroids (use UNK)	RUNX1/ DNMT3A	Yes, pericardial and pleural effusions (cytology positive for AML blasts)
		1091 -027	21 M/MRD	Responded	6	Hx of Gr 1 GVHD of skin	KMT2A	No

Note: The **red text** signifies adverse risk patient characteristic.

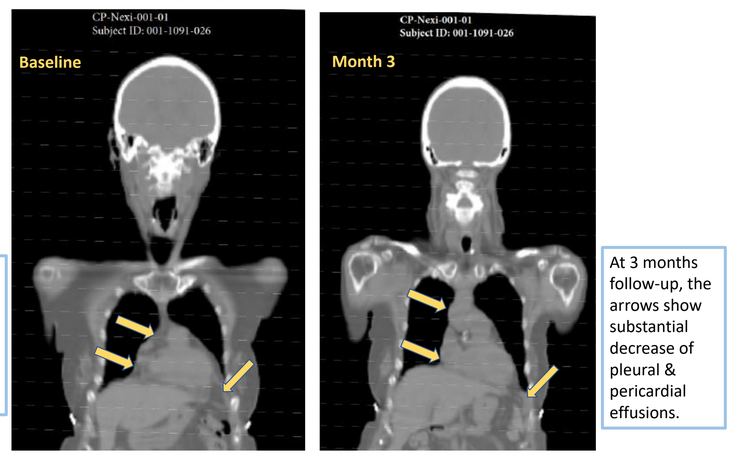
- Most of the patients had 3 to 4 adverse risk patient characteristics.
- 9 of 11 (82%) patients had adverse risk mutations at diagnosis.
- 7 of 11 (64%) patients had AML that was refractory to induction therapy.
- 7 of 11 (64%) patients had post-allo HCT remission < 12 months.
- 3 of 11 (27%) patients had primary or secondary extramedullary disease.

Main Conclusions:

- Early results suggest that antigen-specific NEXI-001 T cells have the potential to enhance GVL effects in relapsed/refractory patients post allo-HCT.
- NEXI-001 was well-tolerated with easily manageable side effects.
- Increased clinical activity has been observed with increasing NEXI-001 T cell doses up to a 600 M total dose (200 M weekly x 3).
- NEXI-001 antigen-specific T cells persisted and maintained memory subtypes in peripheral blood and bone marrow up to at least 9 months (to date) suggesting that a 600M dose 1-2 cycles may lead to responses across heterogenous adverse risk patients.
- The data support the continuation of the study to include the Expansion Stage to gain further safety experience and a more complete assessment of clinical activity.

Results – Clinical Activity Data:

- 10 of 11 of these poor prognostic patients did not achieve a remission to their last salvage therapy prior to study enrollment.
- Neutrophil and platelet count increases associated with decreases in blasts in peripheral blood and/or bone marrow.
- Cohort 2 Patient 001-1091-017 (single cycle of 2x10^8 NEXI-001 T cells):
  - Achieved an MRD(-) remission following bridging therapy
  - After receiving NEXI-001 T cells, **remained in CRMRD(-) for up to 9 mo.**
- Cohort 3 Patient 001-1091-026 (2 x 10^8 NEXI-001 T-cells on Days 1, 8, and 15):
  - At baseline, extramedullary disease relapse manifested by a large symptomatic pleural & pericardial effusions (cytology positive for leukemic blasts).
  - After the administration of NEXI-001 T cells, **achieved a decrease to a small asymptomatic pleural effusion**. A PET/CT scan of the chest showed **no areas of increased uptake in soft tissue** that would indicate disease involvement.
  - The patient has **remained asymptomatic at 3 months of follow up** with no detectable AML blasts in peripheral blood or bone marrow.

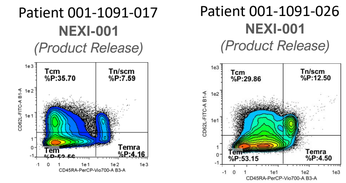


At baseline, the arrows show areas of marked pleural & pericardial effusions.

At 3 months follow-up, the arrows show substantial decrease of pleural & pericardial effusions.

Results - Antigen Specificity & Immunophenotyping:

- The NEXI-001 product contains T cells of early memory phenotype including stem cell-like memory, central memory, and effector memory CD8⁺ T cells.



- Antigen-specific T cells persisted and expanded in peripheral blood and trafficked to bone marrow, maintaining important memory subtypes.
- Percent of antigen-specific T cells increases with increasing dose of NEXI-001 infusion in peripheral blood and bone marrow.

Total Antigen Specificity (% of CD8⁺ T cells)				
	Cohort 2 Patient 001-1091-017		Cohort 3 Patient 001-1091-026	
	Visit	Total Specificity	Visit	Total Specificity
PBMC	M1	5.86	M1	14.54
	M3	9.10	M3	14.66
BMMC	M1	33.86	M2	**83.75**
	M3	51.89	M3	**72.23**

Results – Safety Data:

- No dose-limiting toxicities & no ICANS have occurred in Cohorts 1, 2 & 3.
- No patients died or discontinued due to a treatment-emergent adverse event (TEAE).
- NEXI-001 related TEAEs included: 2 patients each with CRS & GVHD; 1 patient each with pyrexia, nausea, diarrhea, headache, peripheral sensory neuropathy, hypoxia, hyperhidrosis (IRR), flushing (IRR), hypotension, and orthostatic hypotension.
- AEs of Special Interest:
  - 1 patient with Gr 3 GVHD, with gut involvement (reported as related SAE) resolved w/in 72 hrs (note the patient had history of GVHD); 1 patient with Gr 1 GVHD (skin-related).
  - 2 patients with CRS (both non-serious; symptoms of hypotension & hypoxia for 1 patient, and fever & tachycardia for 1 patient).

Future Directions for Research:

- These findings warrant further study of the NEXI-001 T cell product as salvage therapy for patients with relapsed AML following allo-HCT.
- Combination studies with bispecific T-cell engagers and/or checkpoint inhibitors are under consideration.
- Patients to receive additional cycles beyond cycle 1 to enhance GvL effect.