A PHASE 1 STUDY OF NKX101, A CHIMERIC ANTIGEN RECEPTOR NATURAL KILLER (CAR-NK) CELL THERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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INTRODUCTION

Patients with relapsed or refractory (r/r) acute myeloid leukemia (AML) are unlikely to achieve subsequent complete response (CR), with a historical control CR rate of ~ 20%.[1,2]

Recent progress has been limited to targeted therapies, only benefitting a small subset of the population. Efforts to develop cellular therapies have met with challenges related to the absence of a biologically dispensable target.

NKG2D is a key activating NK cell receptor and the interaction of NKG2D and NKG2D ligand on AML blast cells is hypothesized to eradicate tumor cells.[3]

NKX101 is an NK cell therapy derived from healthy donors and engineered to express an NKG2D ligand-directed chimeric antigen receptor (CAR) to enhance killing of malignant cells, as well as a membrane bound form of interleukin (IL)-15 to improve persistence and activity.[4]

AIM

Safety and preliminary anti-tumor activity were evaluated in patients with r/r AML given a lymphodepletion (LD) regimen consisting of fludarabine and cytarabine (Flu/Ara-C) followed by NKX101.

As Ara-C is known to upregulate NKG2D ligand expression,[5] use of Flu/Ara-C as an alternative to standard Flu/cyclophosphamide (Flu/Cy) for LD was tested with NKX101.

METHODS

Six patients with r/r AML were initially enrolled in this cohort of NKX101-101, a Phase 1 safety study (NCT04623944). All patients had received at least one prior line of therapy. Patients received NKX101 at a dose of 1.5^9 viable CAR+ cells on each of Days 0, 7, and 14 after LD with Flu (30 mg/m^2) and Ara-C (2 g/m^2) daily for five days.

Additional treatment cycles were allowed to deepen or consolidate responses.

RESULTS

Baseline Characteristics	N=6
Age, median (range)	62 (27 - 70)
Baseline ECOG, n (%)	
0-1	5 (83%)
2	1 (17%)
Baseline blast %, median (range)	
Marrow	35 (20 – 86)
Peripheral blood	19 (8 – 79)
AML Risk Category, n (%)	
Intermediate	1 (17%)
Poor/adverse	5 (83%)
Prior lines of therapy, median (range)	2 (1 – 3)
Prior venetoclax, n (%)	6 (100%)
Prior Ara-C, n (%)	3 (50%)
Prior HCT, n (%)	2 (34%)

Table 1. At baseline, five out of six patients had poor-risk genetic features, including TP53 mutation. Patients received a median of two prior lines of therapy, with all patients having prior venetoclax (ven) exposure and three out of six patients with prior Ara-C. Two patients had prior HCT with disease relapse within 6 months.

Grade 3 or Higher Treatment Emergent AE Reported in >1 Patient	N=6
Patients with any grade 3 or higher AEs	**6 (100%)**
Anemia	3 (50%)
Sepsis*	3 (50%)
Febrile neutropenia	3 (50%)
Neutrophil count decreased	3 (50%)
Lymphocyte count decreased	2 (33%)
Platelet count decreased	2 (33%)

Table 2. All patients received at least three doses of NKX101 at 1.5^9 cells/dose. There were no cases of cytokine release syndrome (CRS), immune cell associated neurotoxicity syndrome (ICANS) or graft-versus-host disease of any grade. Myelosuppression and infection were the most common grade 3 or higher treatment emergent toxicities.

*One patient had grade 5 non-treatment emergent E. coli sepsis 36 days after last dose of NKX101 which was not related to NKX101 prior to receiving a second cycle of treatment.

Deep disease control with NKX101 with Flu/Ara-C lymphodepletion

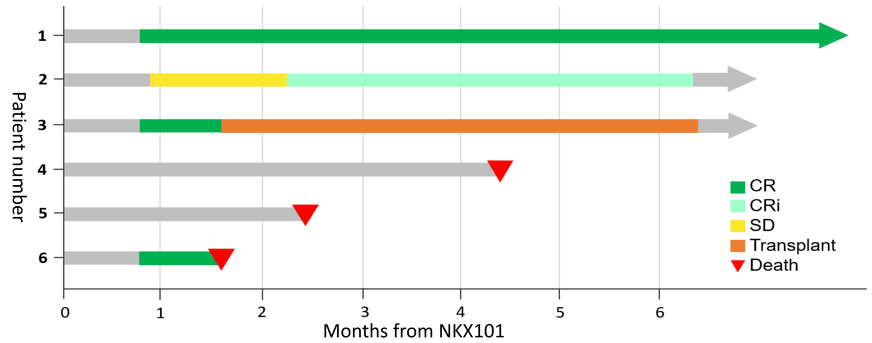

Figure 1. Four of six patients had CR/CRi (67%), with three achieving CR. Patients 1 and 6 had no detectable minimum residual disease (MRD) by flow cytometry after one treatment cycle. Patient 3 had MRD of 0.18% after one cycle and was immediately taken to consolidative hematopoietic cell transplant. Patient 2 had three cycles of treatment with successive decrease in disease burden, resulting in CRi. Data as of October 31, 2023.

Of those who achieved CR/CRi, three out of four remained in CR/CRi at 4 months.

Patient	High risk features	Baseline Marrow Blast Burden	Best Response
1	Relapse <6 mo HCT, TP53 mutation	30%	MRD- CR
2	Relapse <6 mo HCT	30%	MRD- CRi
3	Refractory to multiple cycles of Ara-C	86%	MRD+ CR
4	TP53 mutation	40%	PD
5	Refractory to Ara-C, ven	79%	PD
6	Refractory to ven	20%	MRD- CR

Table 3. High risk characteristics, baseline marrow burden, and best response.

NKX101 PK with Flu/Ara-C Lymphodepletion

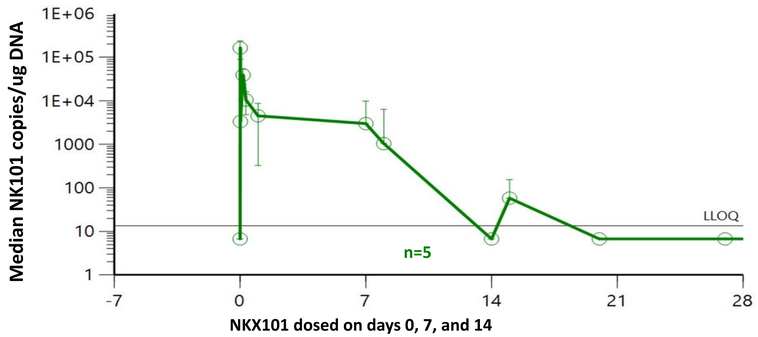

Figure 2. PK profiling showed that NKX101 was consistently detected with clearance after infusion as expected.

CONCLUSIONS

NKX101 shows promising early responses in this group of patients with r/r AML, including those with high-risk features, such as relapse after prior HCT, TP53 mutation, and high blast burden.

The preliminary toxicity profile of this regimen is consistent with underlying AML and exposure to LD, with no events of CRS or ICANS and no deaths related to NKX101.

Enrollment into this cohort is ongoing.

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