Clinical Program Update: NKX101 for Relapsed or Refractory AML

27 June 2023

Clinical Data as of 10 Jun 2023

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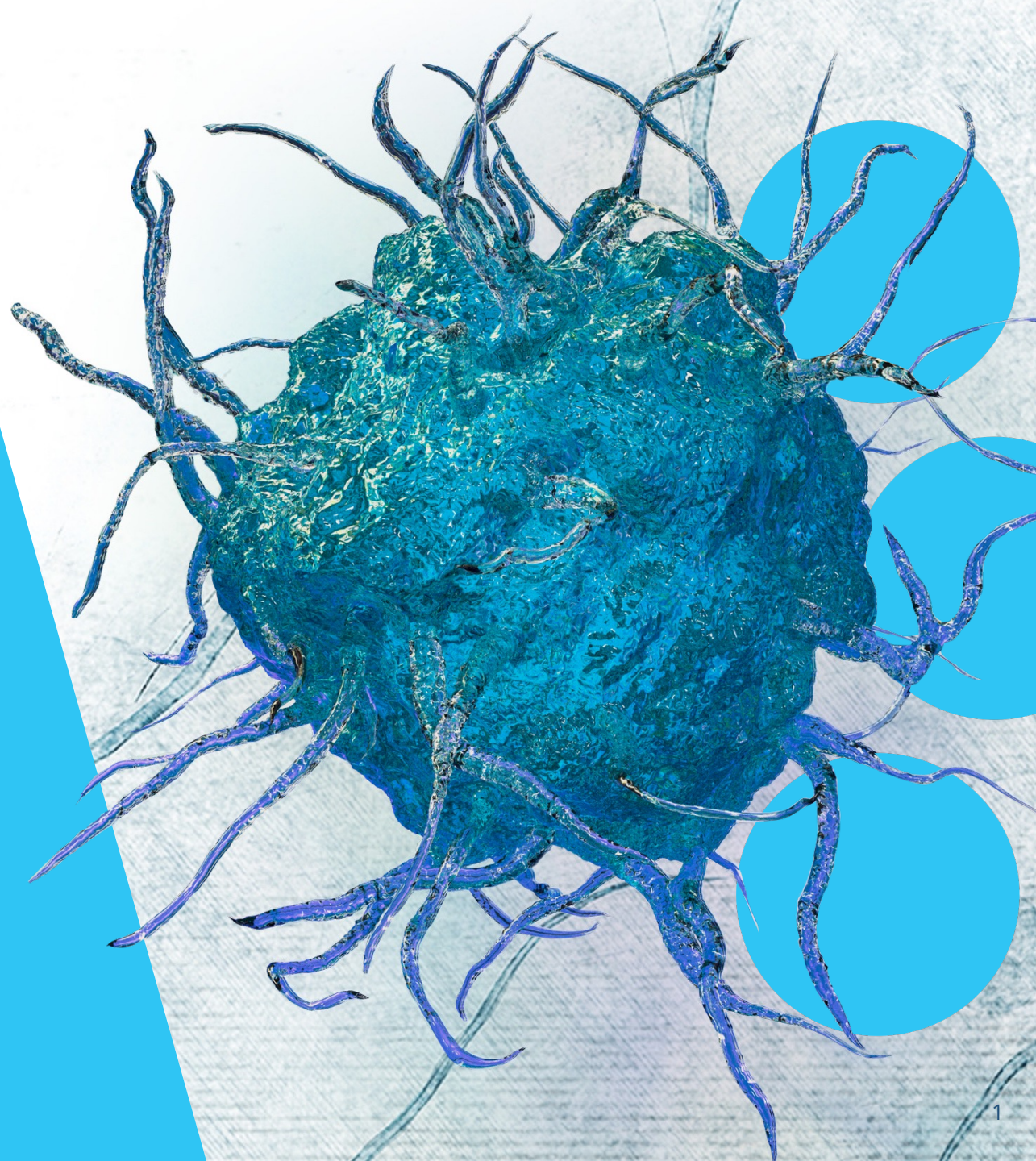

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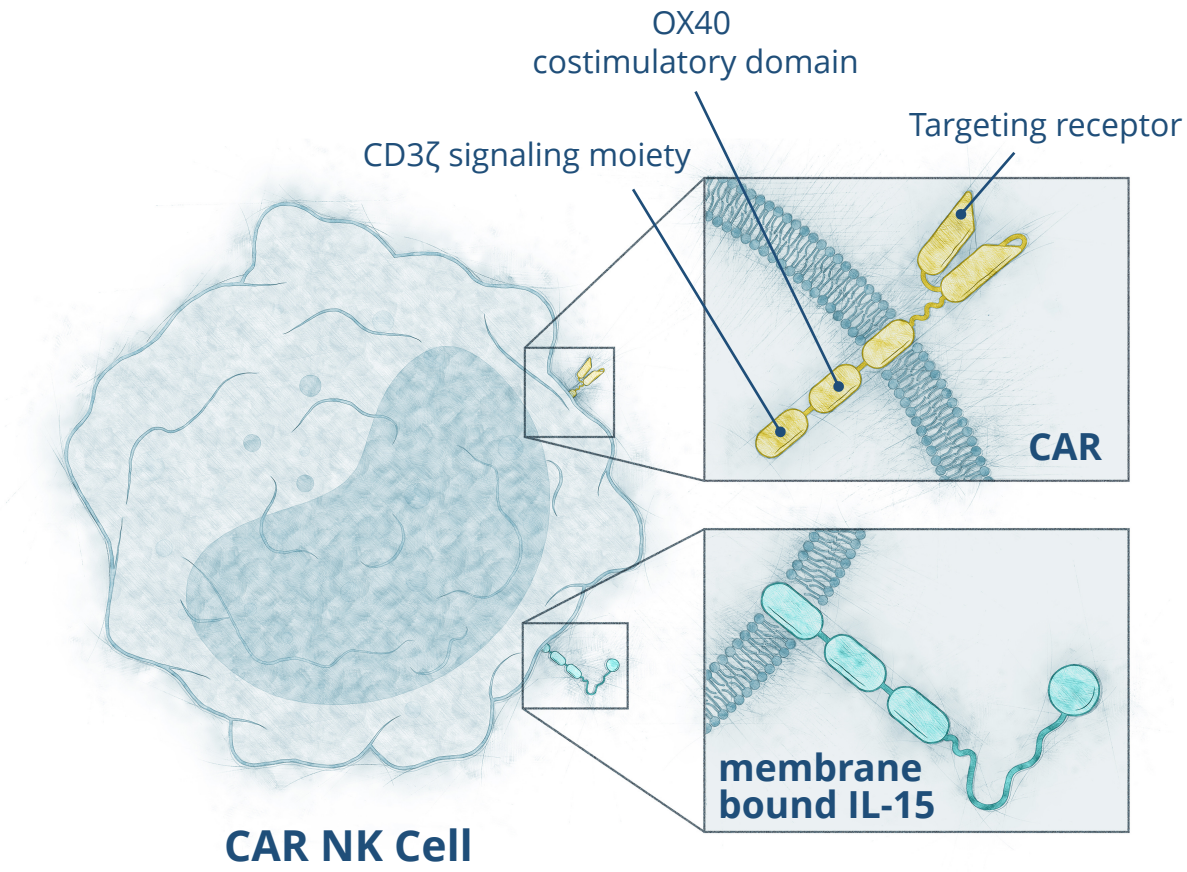
CAR NK cells driving a revolution in off-the-shelf cell therapy

- Next generation platform built for:
  - **Blood cancers and solid tumors**
  - **Allogeneic, off-the-shelf, and on demand**
  - **Industrialized manufacturing**
  - **Outpatient administration**



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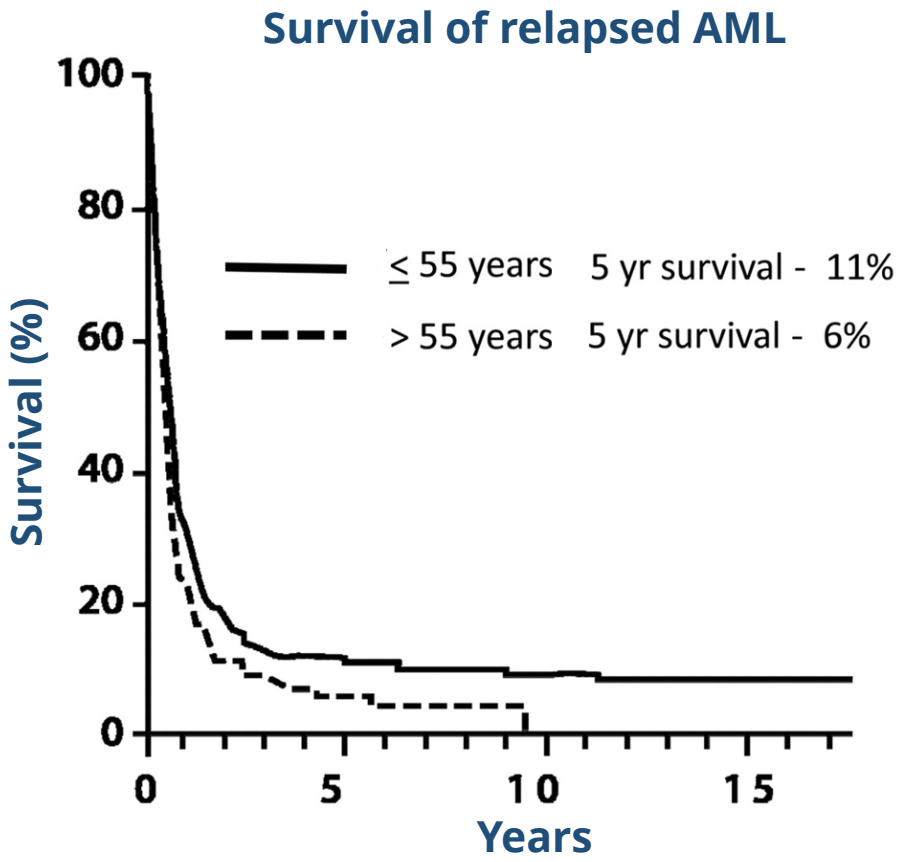
AML is a rapidly progressing leukemia with a poor prognosis

- **Heterogenous group of blood cancers treated with risk-adapted chemotherapy**
  - Most patients will ultimately die from relapse or complications from therapy
- **Outcomes for patients with relapsed or refractory disease are especially poor**
  - Low response rates with standard chemotherapy
  - 12-18% CR rate, including venetoclax-based regimens
- **Allogeneic HCT is best chance of long-term cure**
  - Limited to patients who are fit
  - Pre-transplant CR improves outcomes



Bewersdorf, J, et al. *Haematologica.* 2020.105(11), 2659.
Perl, et al *N Engl J Med.* 2019 Oct 31;381(18):1728-1740.
Roboz, et al *J Clin Oncol.* 2014 Jun 20;32(18):1919-26.
Rowe, et al *Blood.* 2010 116 (17).

AML, acute myeloid leukemia; CR, complete response; HCT, hematopoietic cell transplantation

Biomarkers have driven development of recent AML therapies

- **CAR T cell therapy for AML has been limited by lack of appropriate antigens**
- **Most recent approvals have been targeted therapies using genetic biomarkers**
- **Response rates are limited, even among those few with targetable mutations**

Biomarker	FLT3	IDH1	IDH2
Prevalence in AML	~30%	6-10%	9-13%
Approved targeted therapy	gilteritinib	ivosidenib	enasidenib
CR rate	21%	22%	19%
Estimated CR rate in total AML population	**6%**	**1-2%**	**2-3%**

Mardiana, et al. *Front Oncol*. 2020 May 6;10:69.
Perl, et al *N Engl J Med*. 2019 Oct 31;381(18):1728-1740.
DiNardo, et al. *N Engl J Med* 2018; 378:2386-2398.
Stein, et al. *Blood*. 2017 Aug 10;130(6):722-731.

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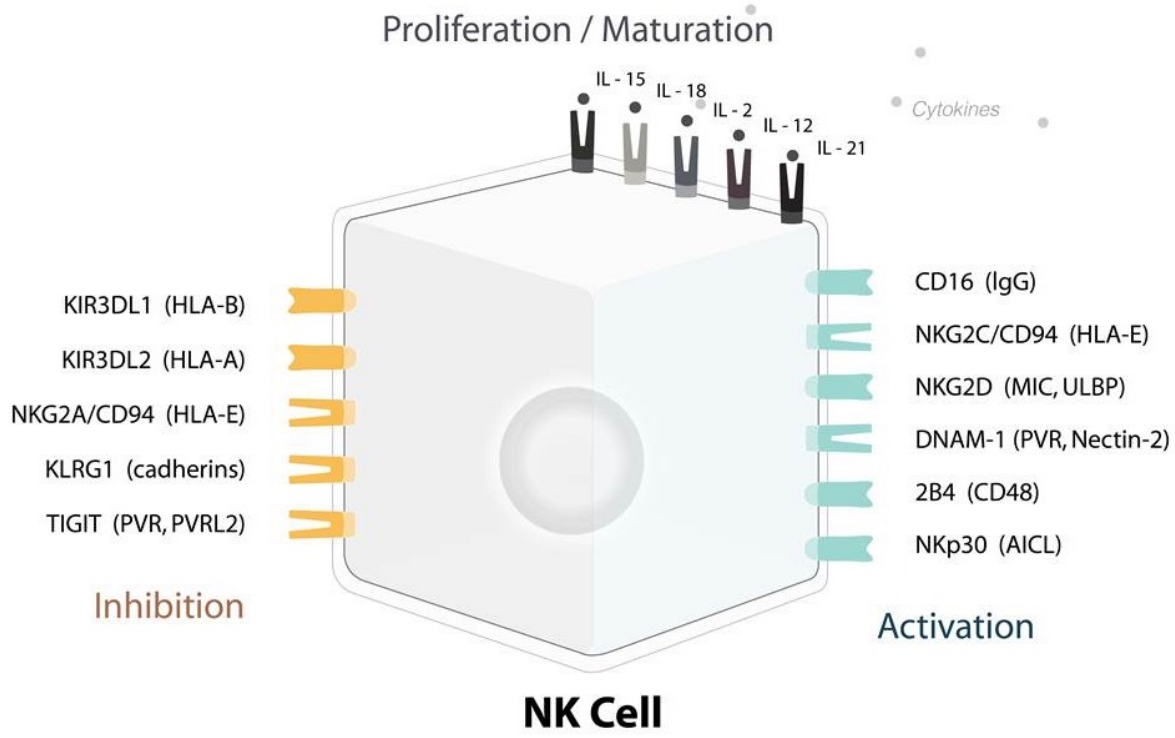
AML, acute myeloid leukemia; CR, complete response; CAR, chimeric antigen receptor.

NK cells have potential for antigen-independent therapy

- **NK cells kill malignant cells through a balance of signals**
  - No need for prior antigen exposure
  - No GVHD due to lack of T-cell receptor
- **NK cell therapy without HCT has been explored in AML for almost 20 years**
  - Well tolerated with limited CRS or ICANS in non-transplant setting
  - CR rate <20% with haploidentical NK cells

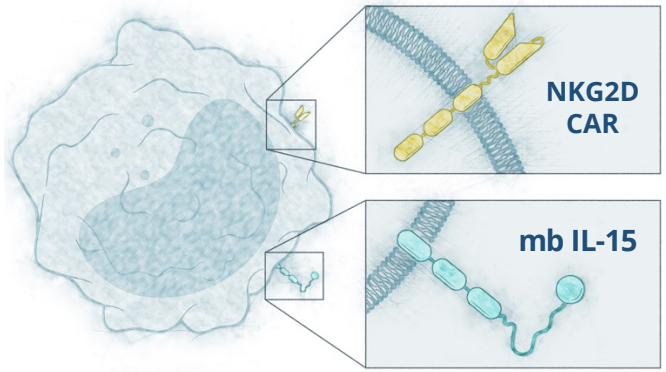


AML, acute myeloid leukemia; CR, complete response; CRS, cytokine release syndrome; HCT, hematopoietic cell transplantation; GVHD, graft-versus-host disease; ICANS, immune effector cell-associated neurotoxicity syndrome; NK cells, natural killer cells

Imai, et al. *Blood*. 2005 Jul 1;106(1):376-83.
Bachier, et al. *Blood*. 2020. 136, Supp 1. 42-43.

NKX101 lymphodepletion with fludarabine/cyclophosphamide

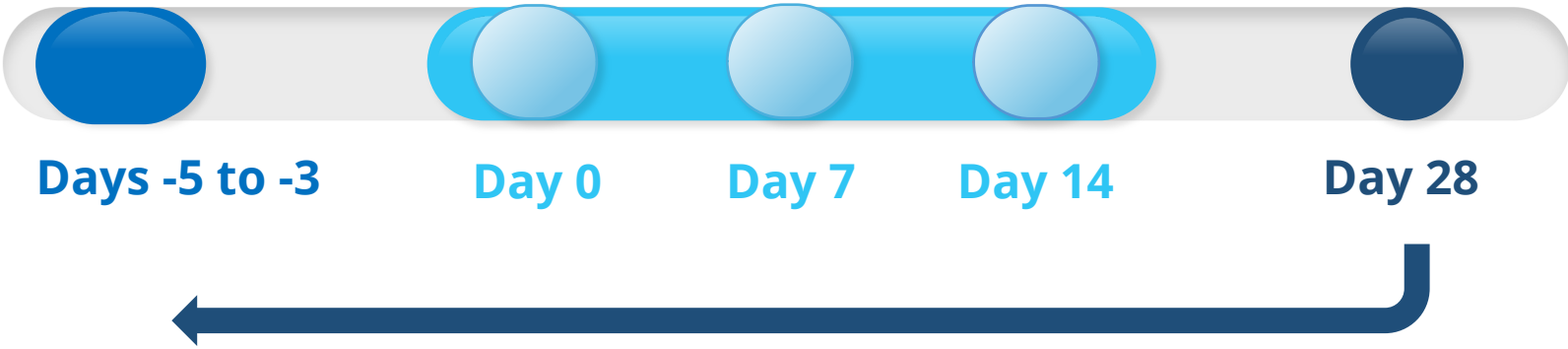
- **High-risk pre-treated patient population**
  - r/r AML ≥1 therapy
  - Must have received approved targeted therapy
  - Pre- and post-BMT



Lymphodepletion
- Cyclophosphamide
- Fludarabine

NKX101 multi-dosing cycle
- 2-3 doses of CAR-NK per cycle

Efficacy assessment
- Based on standard criteria



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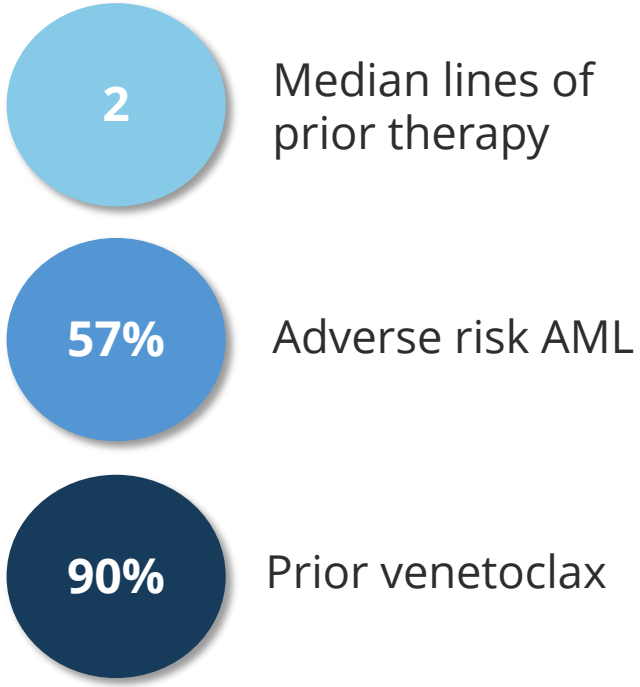
NKX101 patients were multiply-relapsed with poor prognosis

Characteristics	Total (N=30)
Age, median (range)	65 (22 - 81)
Baseline ECOG, n (%)	
0-1	26 (87%)
2	3 (10%)
Baseline marrow blast %, median (range)	18.5 (1 - 85)
AML Risk Category, n (%)	
Favorable	4 (13%)
Intermediate	7 (23%)
Poor/adverse	17 (57%)
Median prior lines of therapy (range)	**2 (1 - 12)**
Prior allogeneic transplant, n (%)	5 (17%)
Prior venetoclax, n (%)	27 (90%)
Prior fludarabine, n (%)	6 (20%)



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ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group.

Based on interim data from open clinical database as of 10 June 2023

NKX101 with Flu/Cy LD was well-tolerated across dose levels

- **No DLTs through 1.5B cells/dose**
- **Myelosuppression and infection consistent with LD and underlying disease were the most common higher-grade toxicities**
- **Limited CAR T-like toxicities**
  - 5 (12%) had infusion reactions, all grade 1/2
  - 5 (12%) patients had CRS, all grade 1/2
  - 1 grade 2 ICANS (Cycle 2)
  - No graft-versus-host disease

Grade 3+ AEs* in ≥10% of patients	Total (n=30)
Hematologic Events	
Thrombocytopenia	18 (60%)
Anemia	16 (53%)
Neutropenia	13 (43%)
Febrile neutropenia	8 (27%)
White blood cell count decreased	5 (17%)
Leukocytosis	4 (13%)
Infections	
Pneumonia	3 (10%)
Other	
Hypoxia ^	4 (13%)
Fatigue	3 (10%)
Hypotension	3 (10%)

** Treatment emergent adverse events regardless of relationship*
^ In the setting of febrile neutropenia/pneumonia

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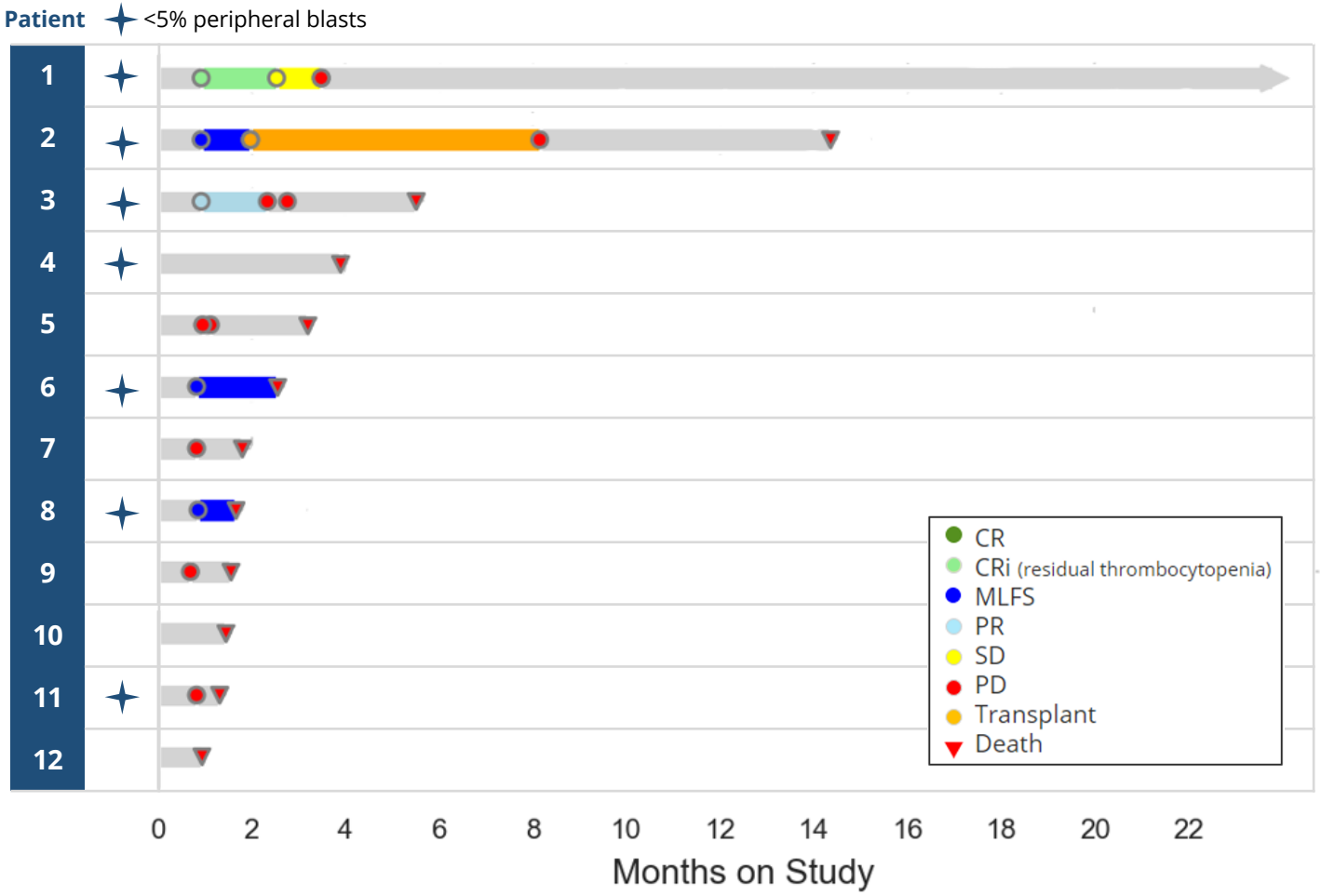
CRS, cytokine release syndrome; DLT, dose limiting toxicity; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome; LD, lymphodepletion

Based on interim data from open clinical database as of 10 June 2023

Response to NKX101 after Flu/Cy lymphodepletion – Early cohorts



- **Previously presented patients with AML treated in cohorts prior to 1B cells/dose x 3**
  - 100M / 300M x 3 doses
  - 150M / 1.5B x 2 doses
- **Response appeared more consistent in those patients with <5% blasts in blood**
  - Marrow blasts: 3-40%
  - ~50% of patients with r/r AML

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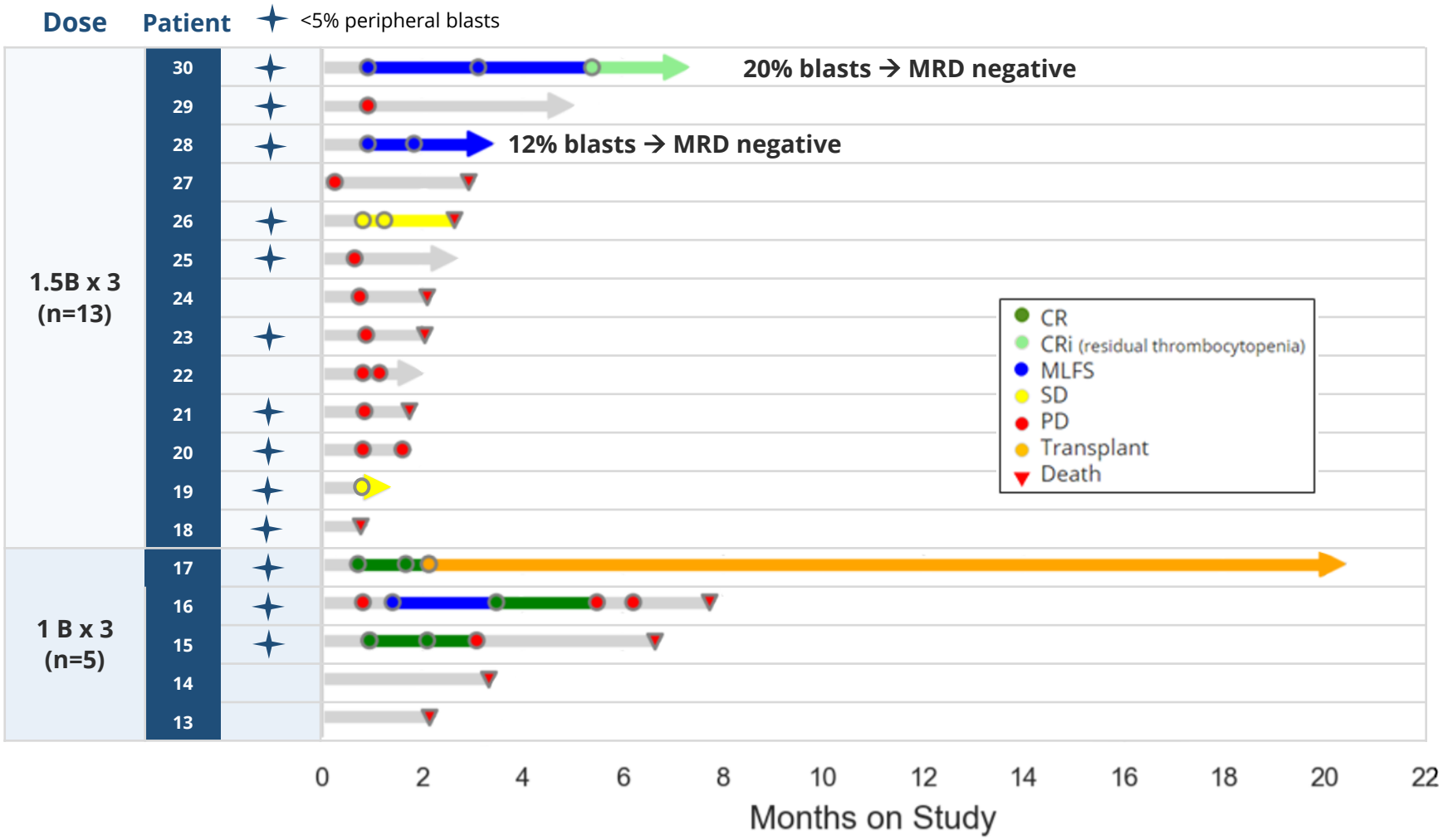
CNS, central nervous system; CR, complete response; CRi, CR with residual thrombocytopenia; HCT: hematopoietic stem cell transplant; MRD, minimal residual disease; MLFS, morphological leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.

Koschade, et al. Ann Hematol. 2022 Aug;101(8):1703-1710.

Based on interim data from open clinical database as of 24 June 2023

Response to NKX101 after Flu/Cy lymphodepletion (≥1B/dose x 3)



- **13 additional patients with AML**
  - 12 at 1.5 B x 3 cell dose
  - 1 at 1 B x 3 cell dose*
- **4/18 (22%) CR/CR$_i$ rate**
  - 3 previously reported CR,
  - 1 new CR$_i$ (MRD negative)
- **Consolidation with HCT has maintained long-term CR**

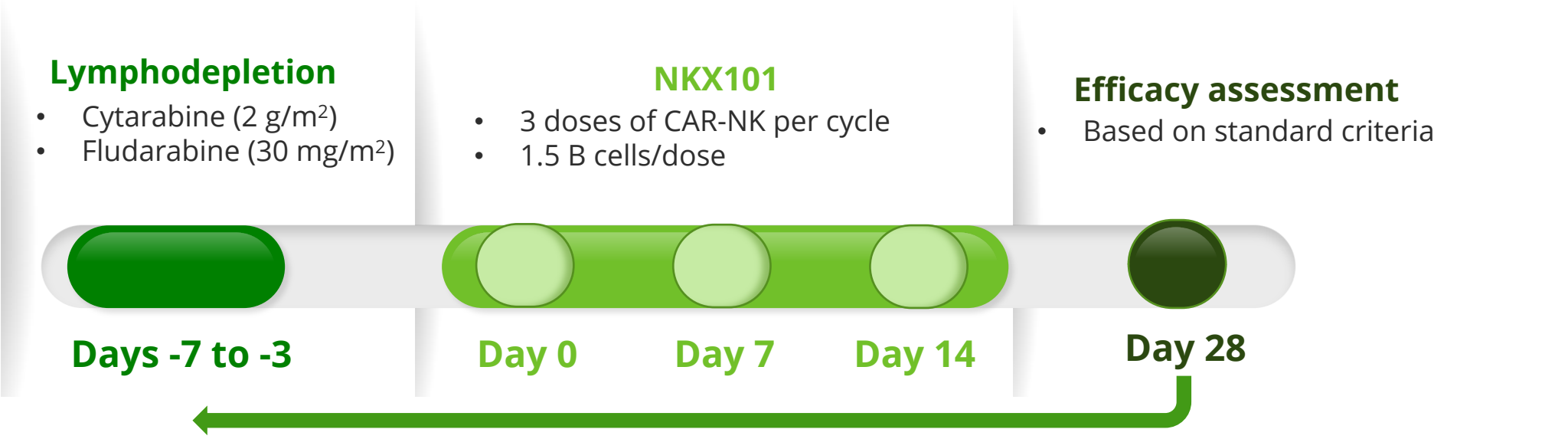
CR, complete response; CRi, CR with residual thrombocytopenia; LD, lymphodepletion; MRD, minimal residual disease; MLFS, morphological leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.

Based on interim data from open clinical database as of 24 June 2023

** Patient was previously reported as diagnosed with MDS in Apr 2022 update*

NKX101 lymphodepletion with Ara-C

- **Fludarabine/Ara-C with anthracycline (e.g. FLAG-Ida) is a frequent salvage regimen for r/r AML with true CR rate of ~10% and cCR rate of ~20% as a comparator arm**
  - Anthracyclines (idarubicin, mitoxantrone, etc) add toxicity and limit addressable population
- **Ara-C (cytarabine) is a DNA damaging agent with potent immunosuppressive effects**
  - Incorporated across AML treatment landscape, including upfront therapy
- **Exposure upregulates NKG2D ligands, increasing sensitivity to NK killing *in vivo***



Roboz, et al *J Clin Oncol.* 2014 Jun 20;32(18):1919-26.
Perl, et al *N Engl J Med.* 2019 Oct 31;381(18):1728-1740.
Holubova, et al. *Int J Mol Sci*. 2019 Jul 15;20(14):3472.
Ogbomo, et al. *Neoplasia*. 2008 Dec; 10(12): 1402–1410.
Cytarabine USPI

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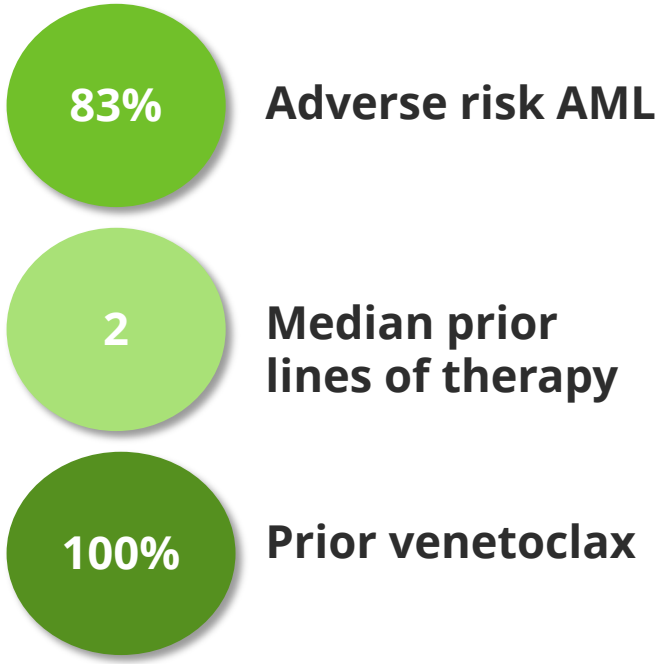
CR: complete response; cCR, cumulative CR rate; FLAG-Ida: fludarabine, cytarabine +/- GCSF and idarubicin; NK: natural killer; NKG2D: natural killer group 2, member D

Demographics for Flu/Ara-C lymphodepletion cohort

Characteristics	Total (N = 6)
Age, median (range)	61.5 (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%)
Median prior lines of therapy (range)	**2 (1 - 3)**
Prior venetoclax, n (%)	6 (100%)
Prior cytarabine, n (%)	3 (50%)



AML: acute myeloid leukemia; ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group.

Based on interim data from open clinical database as of 10 June 2023

Manageable safety profile for Flu/Ara-C lymphodepletion cohort

- **No DLTs (all 1.5B cells/dose)**
- **Myelosuppression and infection were the most common higher-grade toxicities and consistent with LD and underlying disease**
- **No Grade >3 infections**
- **No CAR T-like toxicities**
  - No CRS of any grade
  - No ICANS/neurotoxicity
  - No graft-versus-host disease

Grade 3+ AEs in >1 subject	Total (n=6)
Hematologic Events	
Anemia	3 (50%)
Febrile neutropenia	3 (50%)
Neutropenia	3 (50%)
Thrombocytopenia	2 (33%)
Lymphocyte count decreased	2 (33%)
WBC decreased	2 (33%)
Infections	
Sepsis	3 (50%)

DLT, dose limiting toxicity; LD, lymphodepletion; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, Immune Effector Cell- Associated Neurotoxicity Syndrome; AE, adverse event; WBC, white blood count.

Based on interim data from open clinical database as of 10 June 2023

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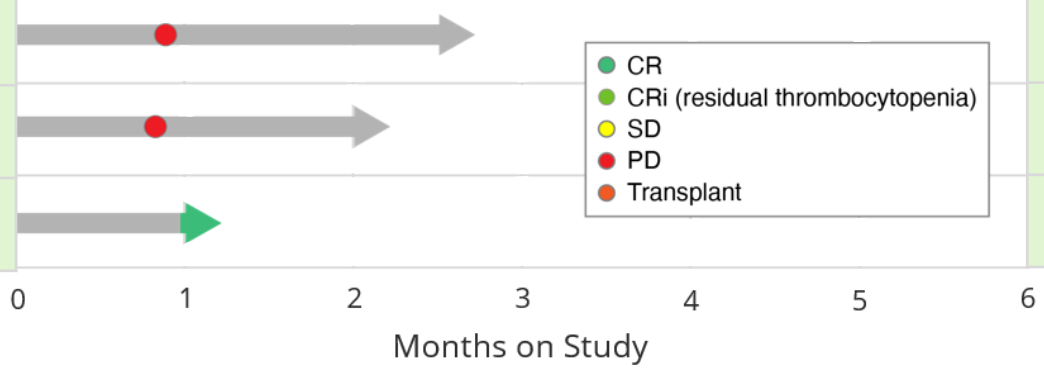
Deep disease control with NKX101 with Flu/Ara-C lymphodepletion

Patient	Patient Info	Marrow Blast	NKX101 Response
1	70 yo ♂ TP53 AML relapse <6 mo post HCT	30%	**CR (MRD negative)** after cycle 1 Consolidated with cycle 2, remains in CR
2	50 yo ♂ WT1 AML relapse <6 mo post HCT	30%	**CRi (MRD negative)** after 3 cycles Response deepened with each of cycle
3	27 yo ♂ AML refractory to 7+3, HiDAC, FLT3 inh	86%	**CR (MRD 0.18%)** after 1 cycle Taken to allogeneic HCT, remains in CR
4	70 yo ♂ AML refractory to ven/aza, CD123 ADC	40%	Progressive disease
5	63 yo ♀ AML, refractory to dauno/Ara-C, dec/ven	79%	Progressive disease
6	60 yo ♀ AML unfit, refractory to dec/ven	20%	**CR, flow negative (MRD pending)** after 1 cycle



- **Deep responses in patients with high-risk clinical features**
  - Early relapse post-HCT
  - Chemo-refractory disease
  - Medically unfit

- **4/6 (67%) CR/CRi rate**
- **3/6 (50%) CR rate**

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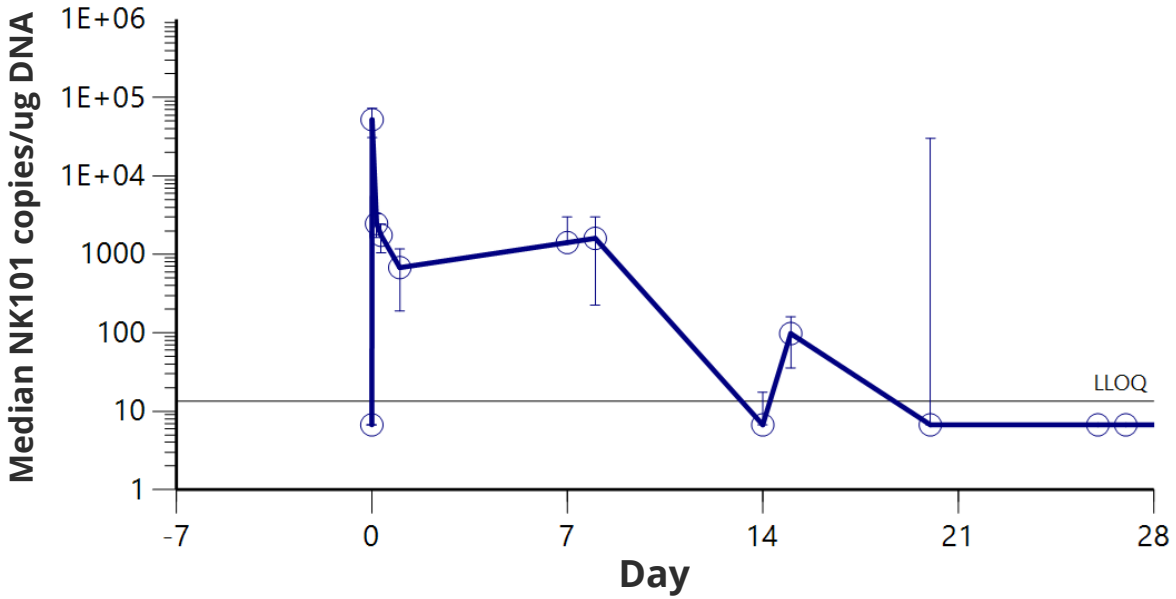
7+3: Cytarabine + anthracycline; HiDAC: high dose Ara-C; dec: decitabine; ven: venetoclax.

Bejanyan, et al *Biol Blood Marrow Transplant. 2015 Mar;21(3):454-9.*
Stone, et al. *Leuk Res. 2019 Jul;82:36-42.*

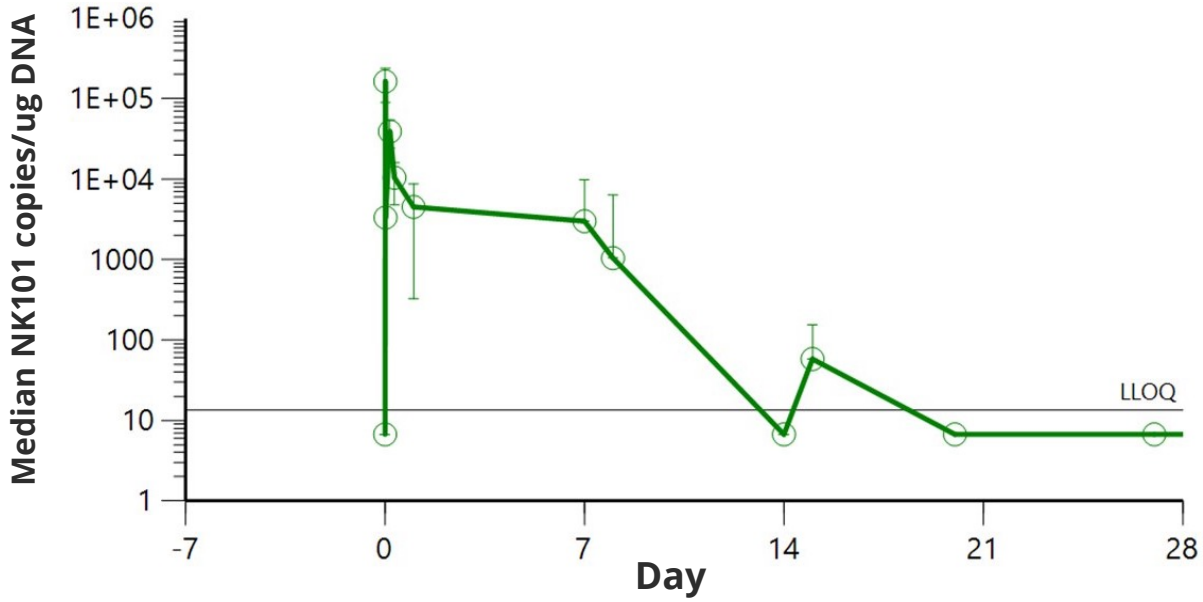
Based on interim data from open clinical database as of 24 June 2023

Ara-C can replace cyclophosphamide without compromising PK

Fludarabine/Cyclophosphamide (n=10)



Fludarabine/Ara-C (n=5)



NKX101 dosed on days 0, 7, and 14

- **Exposure consistent with previously published data using haploidentical NK cells**
- **No need for exogenous IL-2 or other cytokine support**

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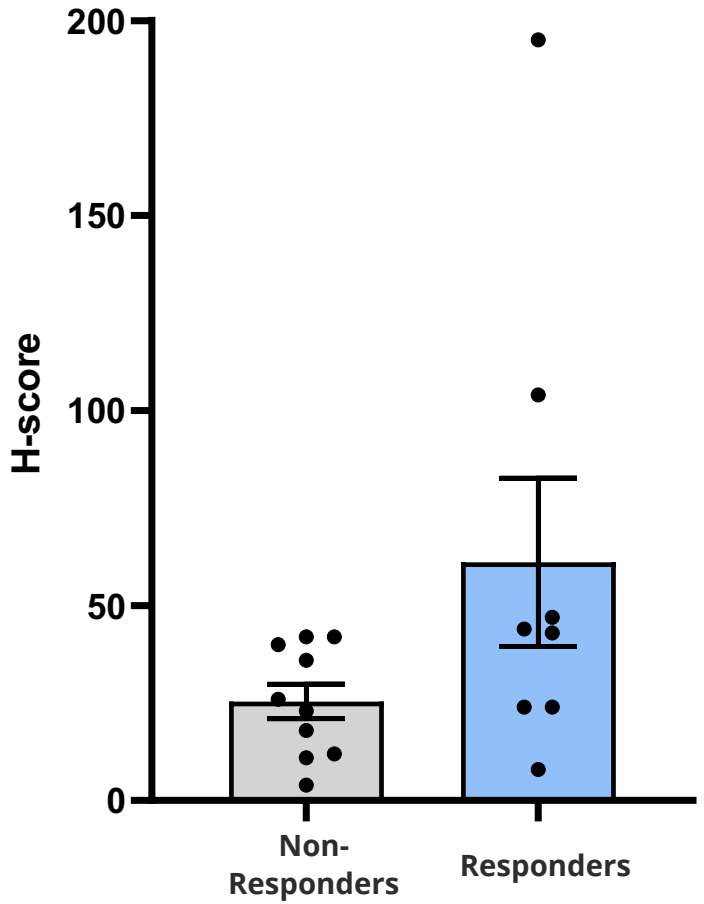
Romee, et al. *Sci Transl Med*. 2016 Sep 21; 8(357)

NKG2D ligands consistently detected in patient bone marrow samples

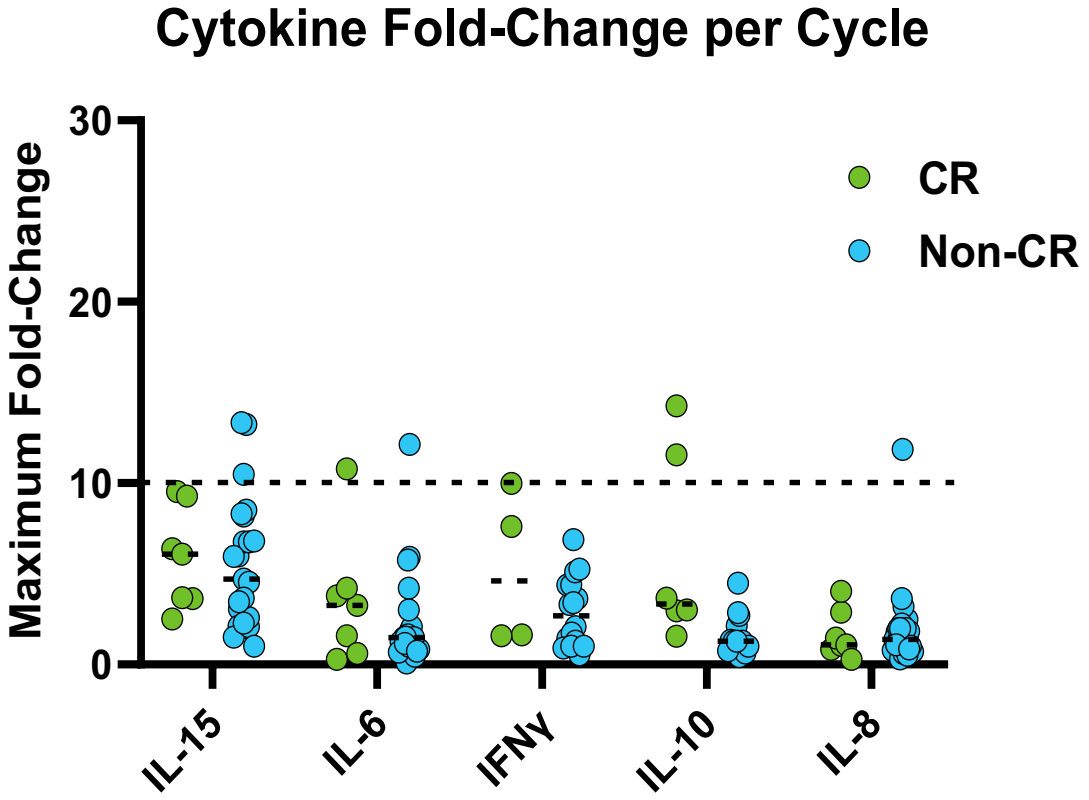
- **Ligand staining via IHC performed on baseline bone marrow samples prior to lymphodepletion and NKX101**
  - MICA/B and ULBP 1/3
  - H-score combines % positive cells and intensity of expression
- **Ligand expression trends higher among responders at higher doses (≥1B)**

All patients at 1B dose and over



Cytokine elevation is modest and not required for clinical response

- **Cytokine levels were measured in patients throughout treatment**
  - Elevation of IL-15, IL-6, IFNγ, IL-10, and IL-8 are all associated with inflammation & CRS
  - Peak levels were only marginally above baseline for most patients
- **Severe CAR T-cell associated CRS can be associated with ~100-fold increases of these pro-inflammatory cytokines**
- **No association was observed between elevated serum cytokines and response to NKX101**



Morris, et al *Nat Rev Immunol*. 2022 Feb;22(2):85-96.
Maude, et al. *Cancer J.* 2014 Mar-Apr; 20(2): 119–122.

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Summary and Next Steps

- **Relapsed/refractory AML is a heterogenous disease with limited therapeutic options**
  - Response rates to traditional chemotherapy remain unacceptably low
  - Approved targeted therapies provide an option for limited number of patients
- **Incorporating Ara-C into NKX101 lymphodepletion provides encouraging antileukemic activity (67% CR/CR_i rate) although follow-up is limited**
  - Cytokines remain low throughout treatment with NKX101, differentiating from CAR T cell therapies
  - Safety profile and pharmacokinetics facilitate moving into earlier lines of therapy with standard of care treatment
- **Next update planned for 1H24**
  - Clinical amendment pending to include consolidation and retreatment
  - Additional enrollment planned in fludarabine / Ara-C cohort