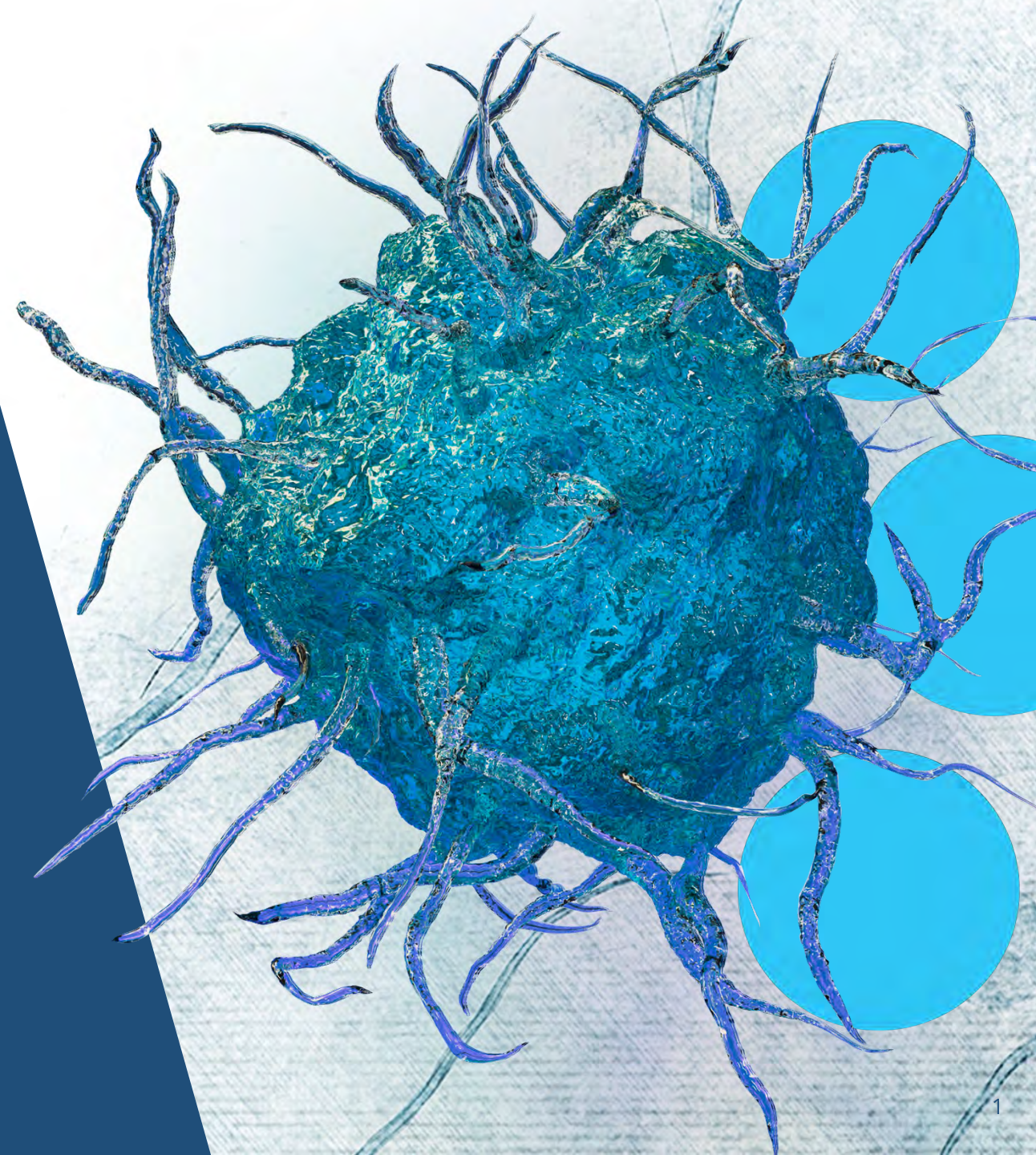


NEXT GENERATION

# Natural Killer Cells

Engineered to Beat Cancer

October 2021



# Forward looking statements

This presentation contains forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, regarding future events and the future results of the company that are based on current expectations, estimates, forecasts, and projections about the industry in which the company operates and the future of our business, future plans and strategies, projections, anticipated trends and events, the economy, and other future conditions, and the beliefs and assumptions of the management of the company. Words such as **“address,” “anticipate,” “believe,” “consider,” “continue,” “develop,” “estimate,” “expect,” “further,” “goal,” “intend,” “may,” “plan,” “potential,” “project,” “seek,” “should,” “target,” “will,”** variations of such words, and similar expressions are intended to identify such forward-looking statements. Such statements reflect the current views of the company and its management with respect to future events and are subject to inherent risks, uncertainties, and changes in circumstances that are difficult to predict and may be outside our control. Therefore, you should not rely on

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# Pioneering the next revolution in cell therapy

Efficient, robust, next generation NK cell platform built for

Blood cancers and solid tumors

Allogeneic and off-the-shelf

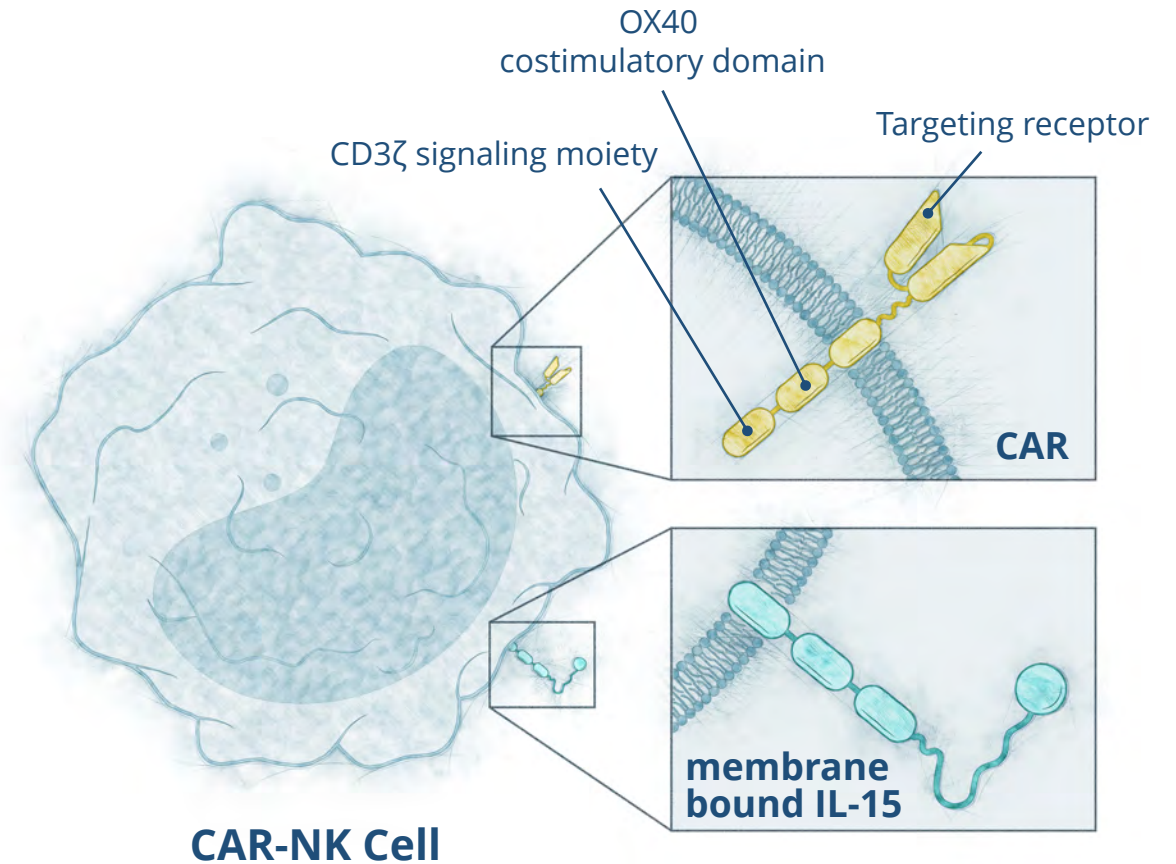
Industrialized manufacturing

Outpatient administration

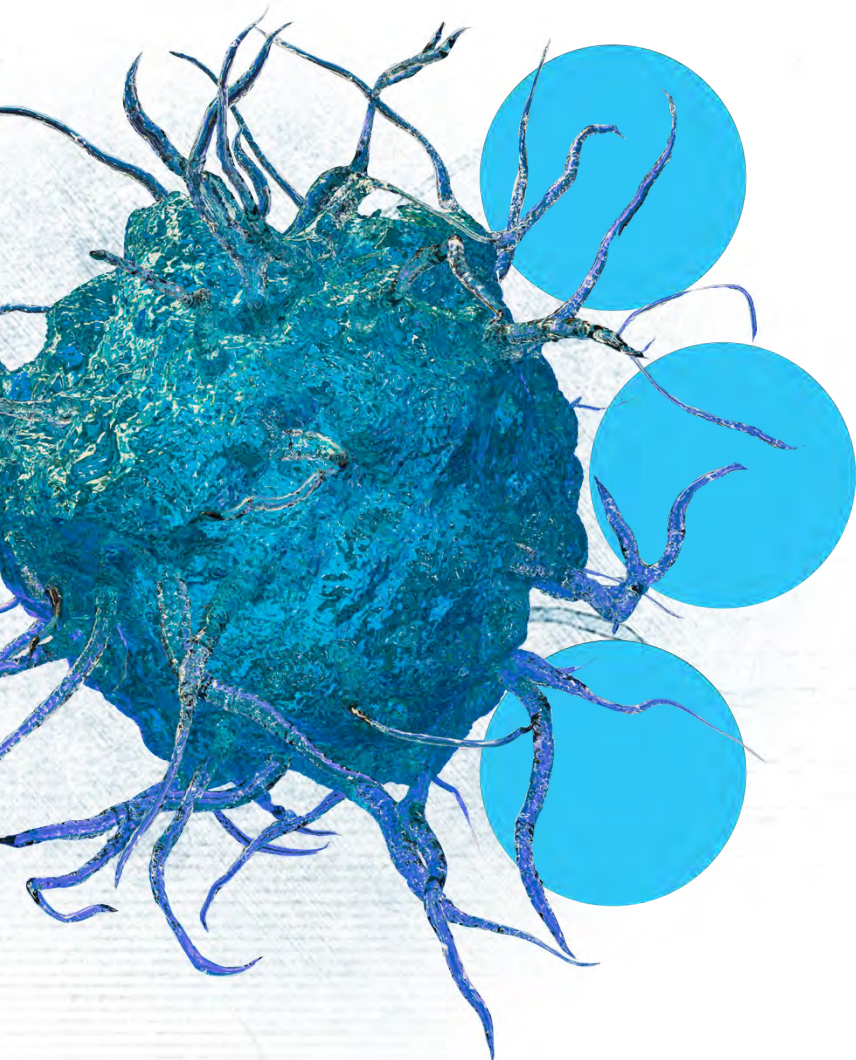
CO-LEAD Clinical Programs

**NKX101**  
NKG2D

**NKX019**  
CD19



# They're called Natural Killer cells for a reason



## Because

Innate power of NK cells to identify and kill transformed cells

Low risk of GvHD

Low risk of CRS and neurotoxicity

Predictable pharmacokinetics

## Therefore

Highly active, cytotoxic cells as foundation and starting material

Naturally allogeneic

Potential for routine administration and broad outpatient access

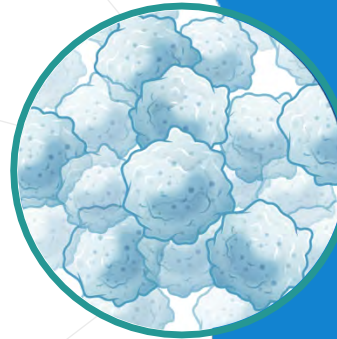
Potential for flexible multi-dose and multi-cycle treatment

# Next gen platform enlists natural, healthy human NK immune cells for optimal product

Donor selection for desired cell features

Process starts with highly active, cytotoxic, NK cells

Multiplex gene engineering to enhance immune cell performance



## Which allows for:



Potential for universal donors and master cell banks



Efficient manufacturing enables rapid, large-scale production



Well defined, high quality, consistent product



Cell therapy  
leaders

Complementary  
expertise

## Global Collaboration to Develop Gene Edited Cell Therapies

### GENOME ENGINEERING CAPABILITY

Best-in-class, clinically validated CRISPR gene editing

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Ability to deploy up to 5 CRISPR/Cas9 gene edits in unlimited number of Nkarta product candidates

### EXPERIENCED CLINICAL DEVELOPMENT PARTNER

Co-development and co-commercialization of CD70 CAR NK, CAR NK + CAR T, and option for a third early-pipeline target program

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Leverage CD70 and allogeneic T cell expertise of CRISPR Therapeutics

## Staying Ahead of the Curve:

## A Platform That Incorporates Multiple **Next Generation** Enhancements

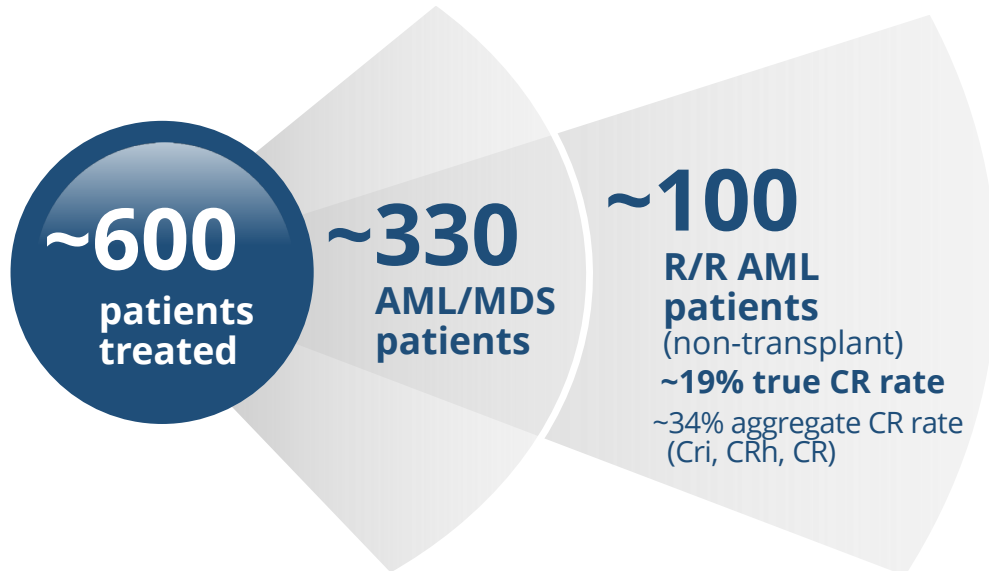
- ✓ Armored cells with membrane-bound IL-15 for persistence
- ✓ Multiplexed CRISPR/Cas9 genome engineering
- ✓ Enhanced expansion, persistence and TME resistance via CISH deletion
- ✓ Cytokine activation using IL-12, -15 and -18 to enhance anti-tumor activity persistence and memory-like properties
- ✓ Clinical trial designs include multi-doses and multi-cycles of treatment
- ✓ No requirement for cytokine support

# Evolving body of clinical data validates NK approach

## NKG2D and non-engineered NK cells – AML

**~30 clinical studies**

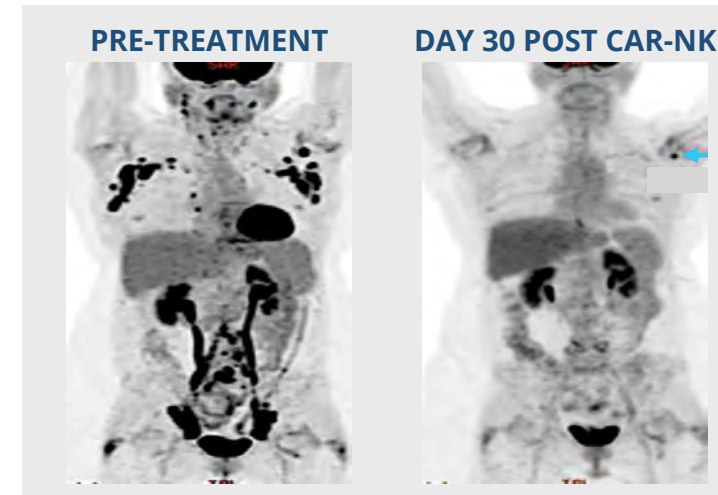
**Well tolerated and no GvHD**  
(non-transplant)



## CD19 – advanced B cell malignancies

**Multiple clinical studies show tolerability and activity of engineered NK cells**

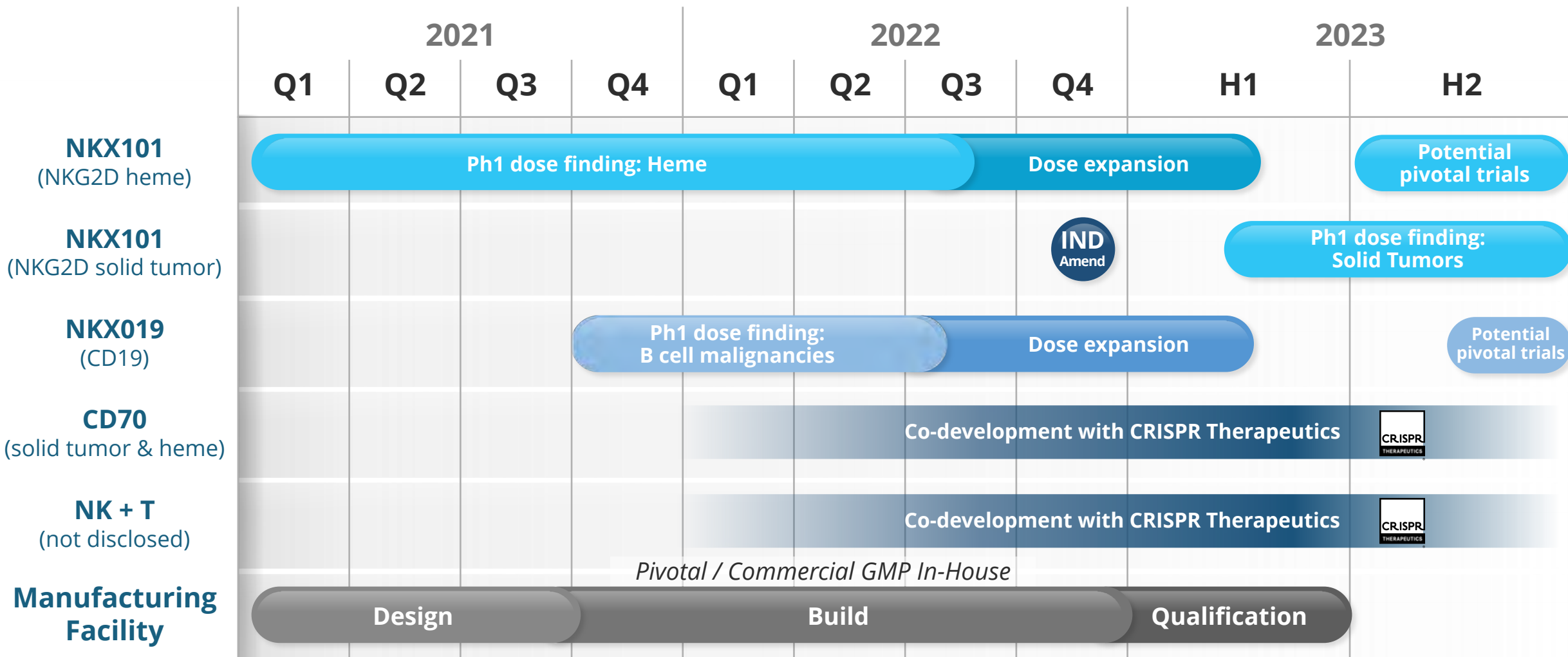
MD Anderson study with CD19 CAR-NK cells  
*New England Journal of Medicine, Feb 2020*



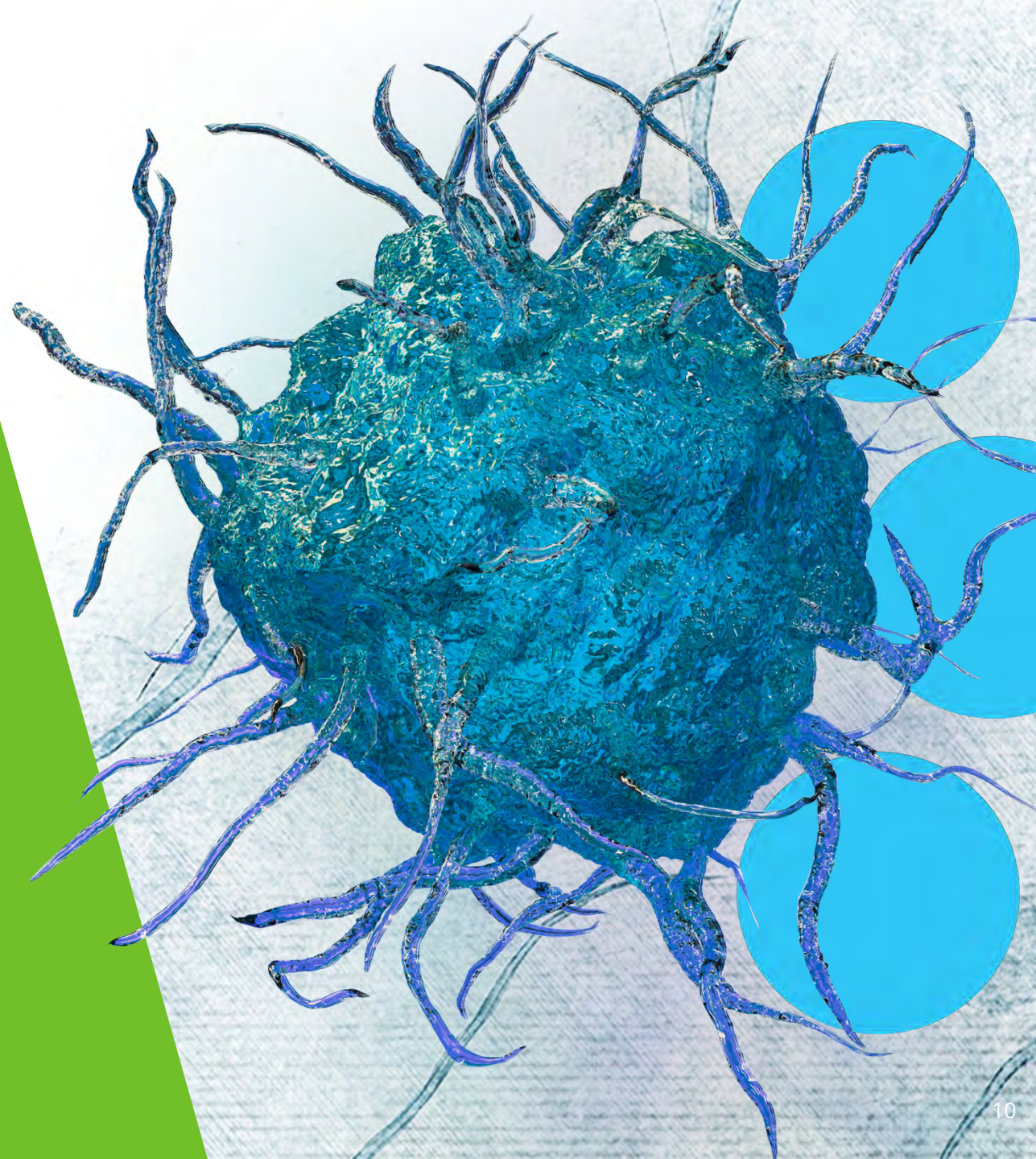
**7 / 11 CRs**

**No reported CRS, GvHD or neurotoxicity**

# Platform-driven pipeline with multiple upcoming milestones



# Platform



# Harnessing the power and efficiency of healthy adult NK cells for the next revolution in cell therapy

FEATURE	CELL SOURCE		
	AUTOLOGOUS	IPSC	DONOR
MANUFACTURING	Highly difficult to scale	Complex NK differentiation and expansion over 4-8 weeks	✓ Robust and scalable 2-week process starting with real NK cells
GENETIC ENGINEERING	Costly and inconsistent	Requires single cell isolation, extensive pre-clinical characterization	✓ Consistent, cost-effective, and efficient
FINAL PRODUCT IDENTITY	Driven by process alone	Sensitive to control of differentiation at scale, subject to genetic drift	✓ Highly consistent NK cell function and phenotype
POTENCY	Variable with starting material; Diminished cell killing capacity due to self recognition and NK cell dysfunction in cancer	Driven by process and genetic engineering	✓ Donor selection, process, and engineering for optimal potency
PACKAGING AND DELIVERY	Limited doses/complex logistics	Cryopreserved and off-the-shelf	✓ Cryopreserved and off-the-shelf

# Proprietary technologies in place for a best-in-class NK cell platform

## Expansion

Donor NK cells are co-cultured with proprietary K562 stimulatory cell line to achieve **high cell numbers**

## Cryopreservation

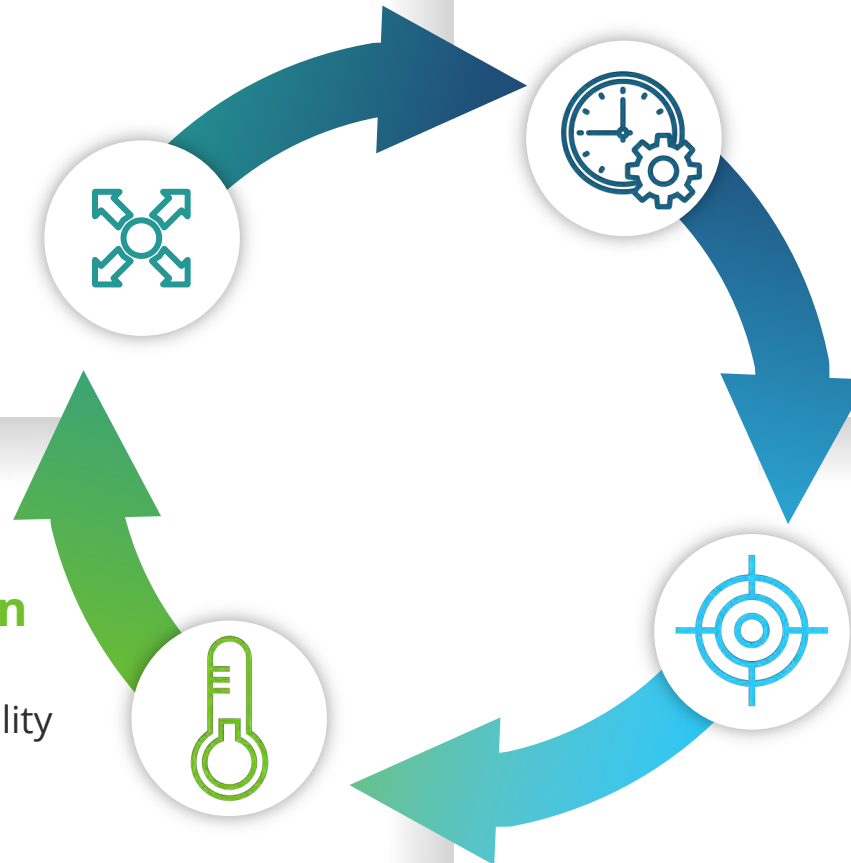
Freezing process maintains NK cell viability and potency to enable true **off-the-shelf cell product**

## Persistence

NK cells are engineered for expression of proprietary **membrane bound IL-15** to enhance time in circulation

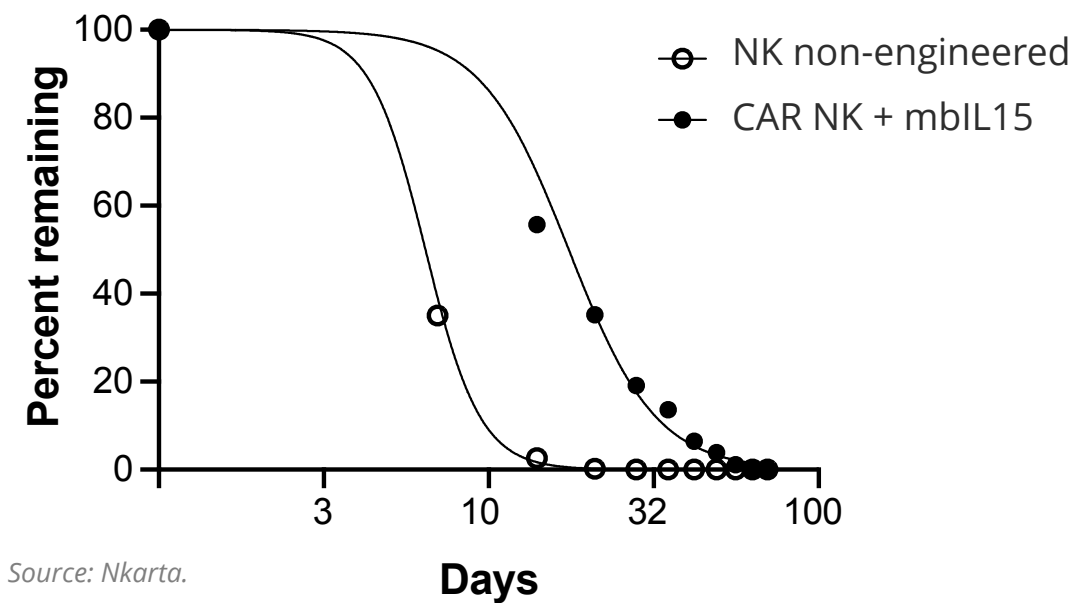
## Targeting

NK cells are engineered for expression of **optimized CARs**



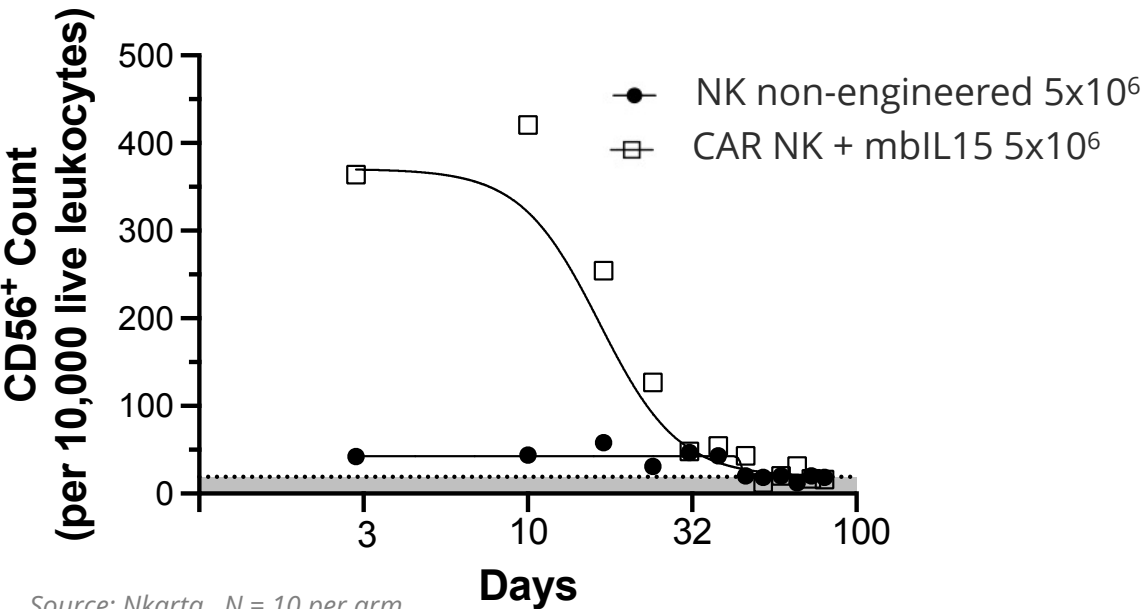
# Superior NK cell persistence from membrane bound IL-15

## IN VITRO PERSISTENCE



2-fold increase in exposure observed in vitro with a single administration

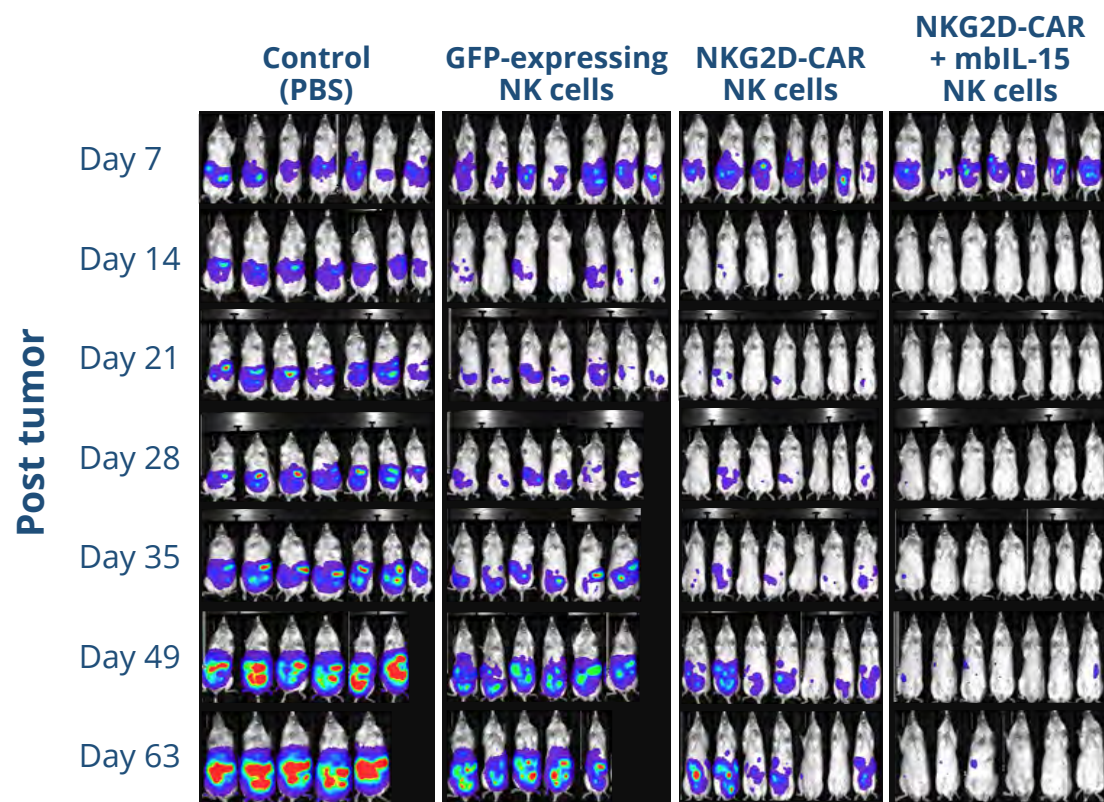
## IN VIVO PERSISTENCE AND EXPANSION IN NSG MICE



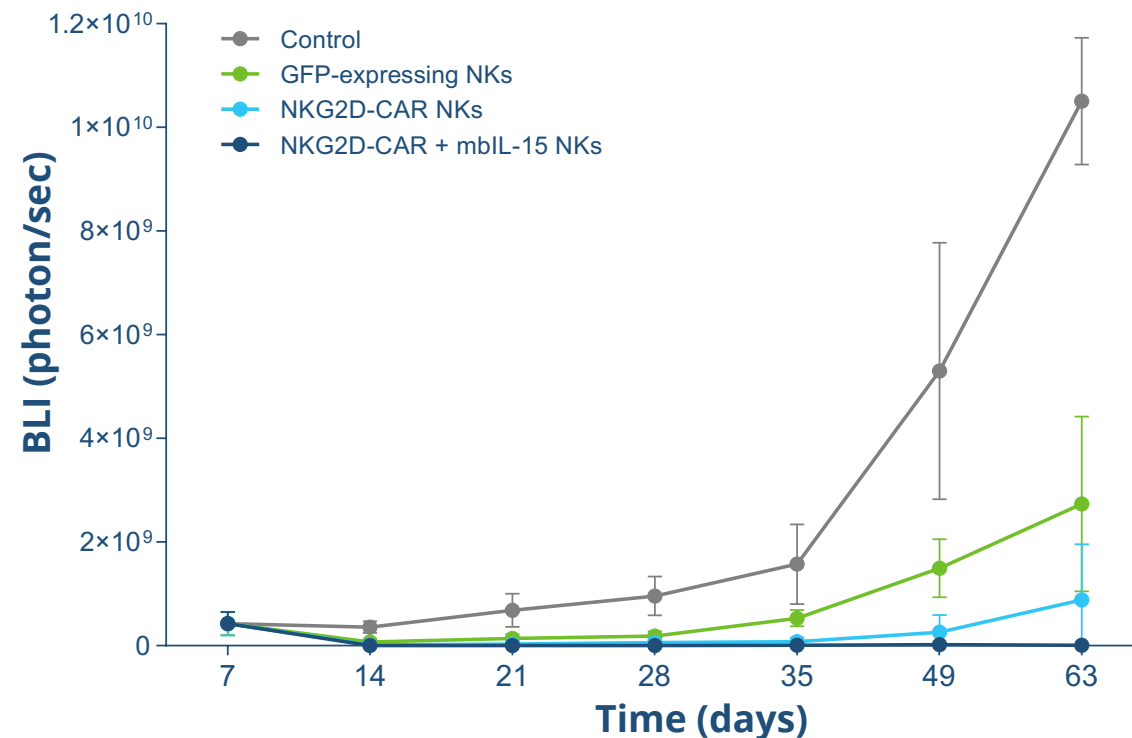
7-fold increase in exposure observed in vivo with a single administration

NK cells engineered to express membrane-bound IL-15 (mbIL-15) demonstrate superior persistence as compared to unmodified NK cells

# Persistence and targeting to maximize anti-tumor activity

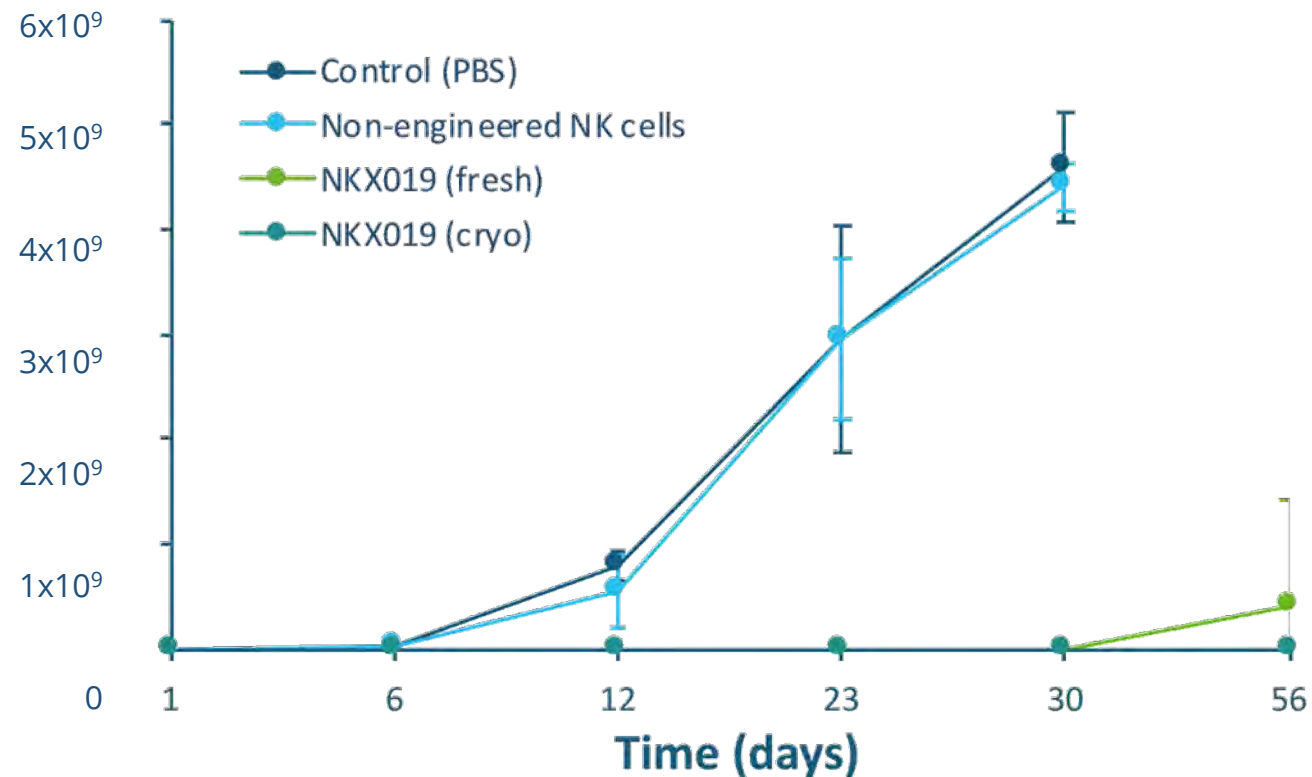
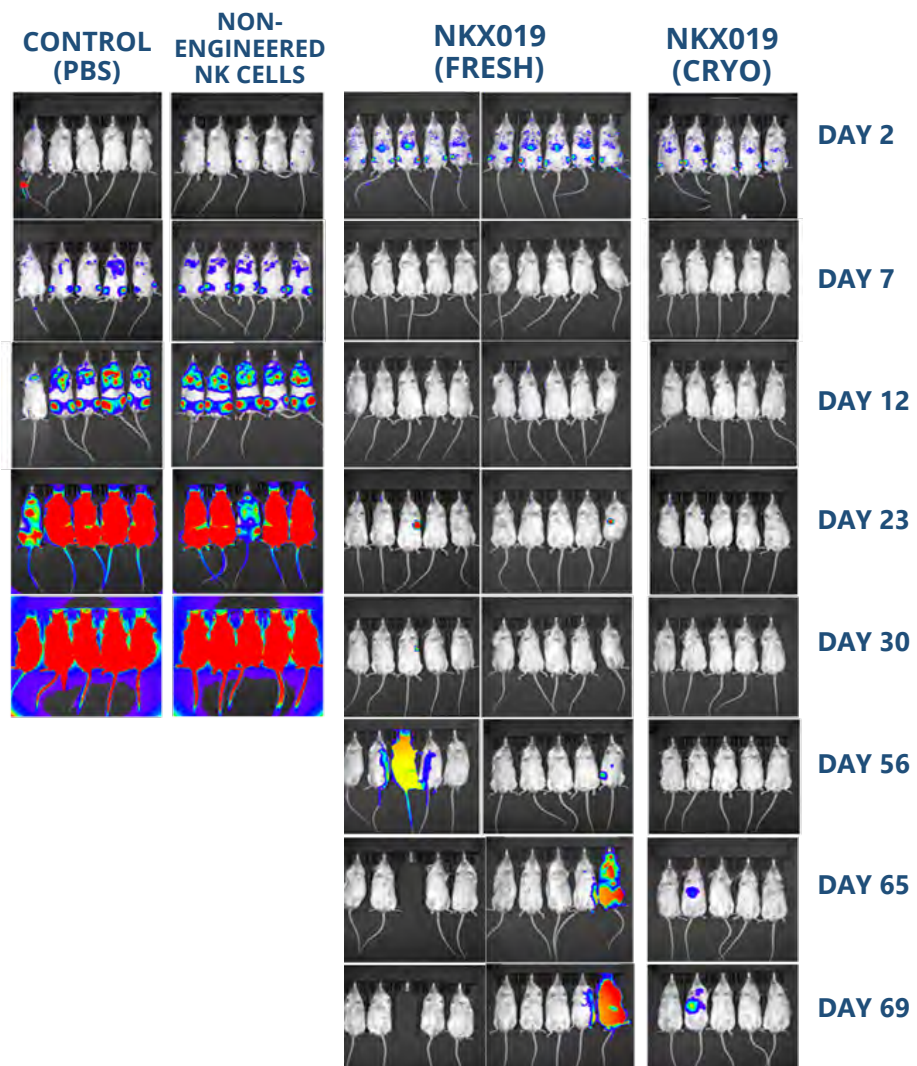


Source: Nkarta. U2OS osteosarcoma model;  $3 \times 10^6$  NK cells administered on D7. Graphical data at right are average BLI of mice above.



**NK cells demonstrate enhanced tumor killing when engineered for targeting and mbIL-15 expression**

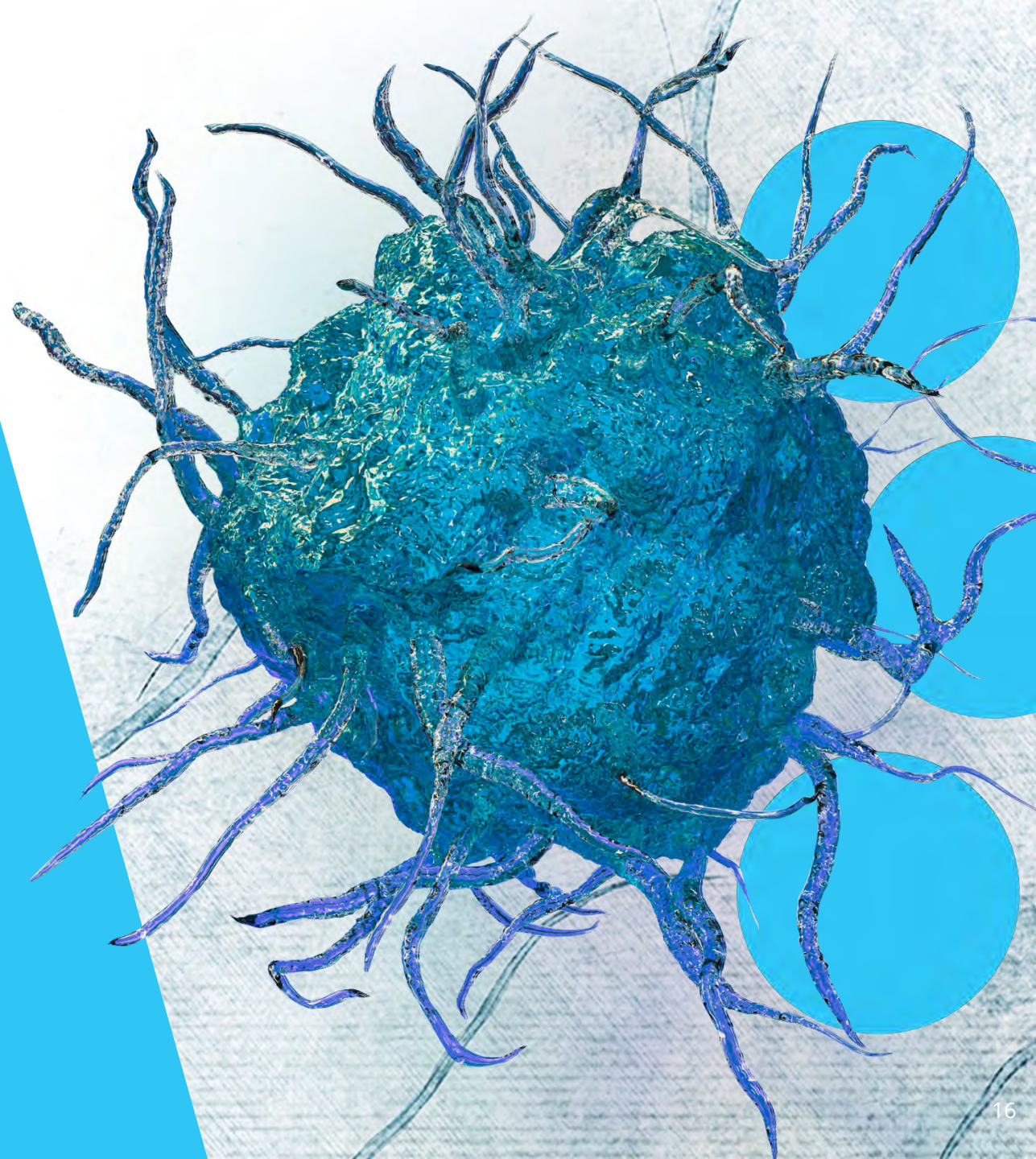
# Our cryopreserved products are highly cytotoxic



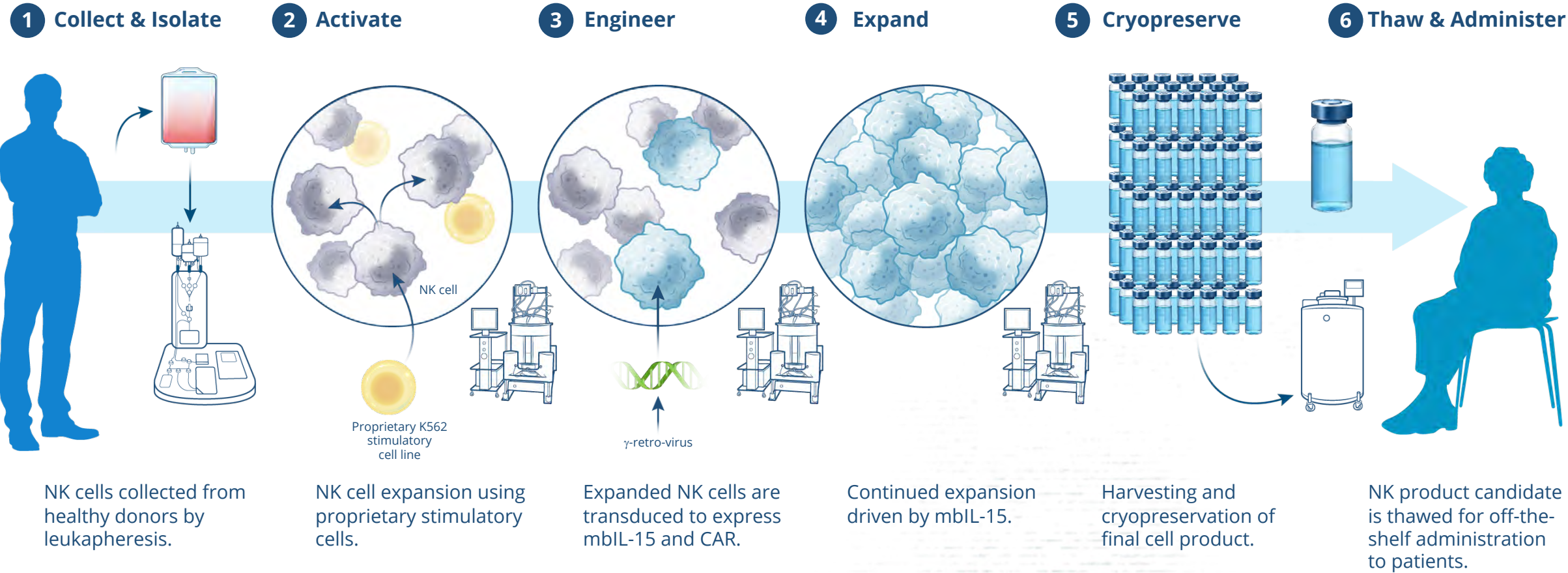
Nalm-6 lymphoma model. 107 cells administered one day post tumor. Graphical data above are an average of mouse luminescence at left. "Cryo" denotes cryopreserved then thawed NKX019.

**NKX019 production under optimized conditions allows cryopreservation with retention of *in vivo* activity**

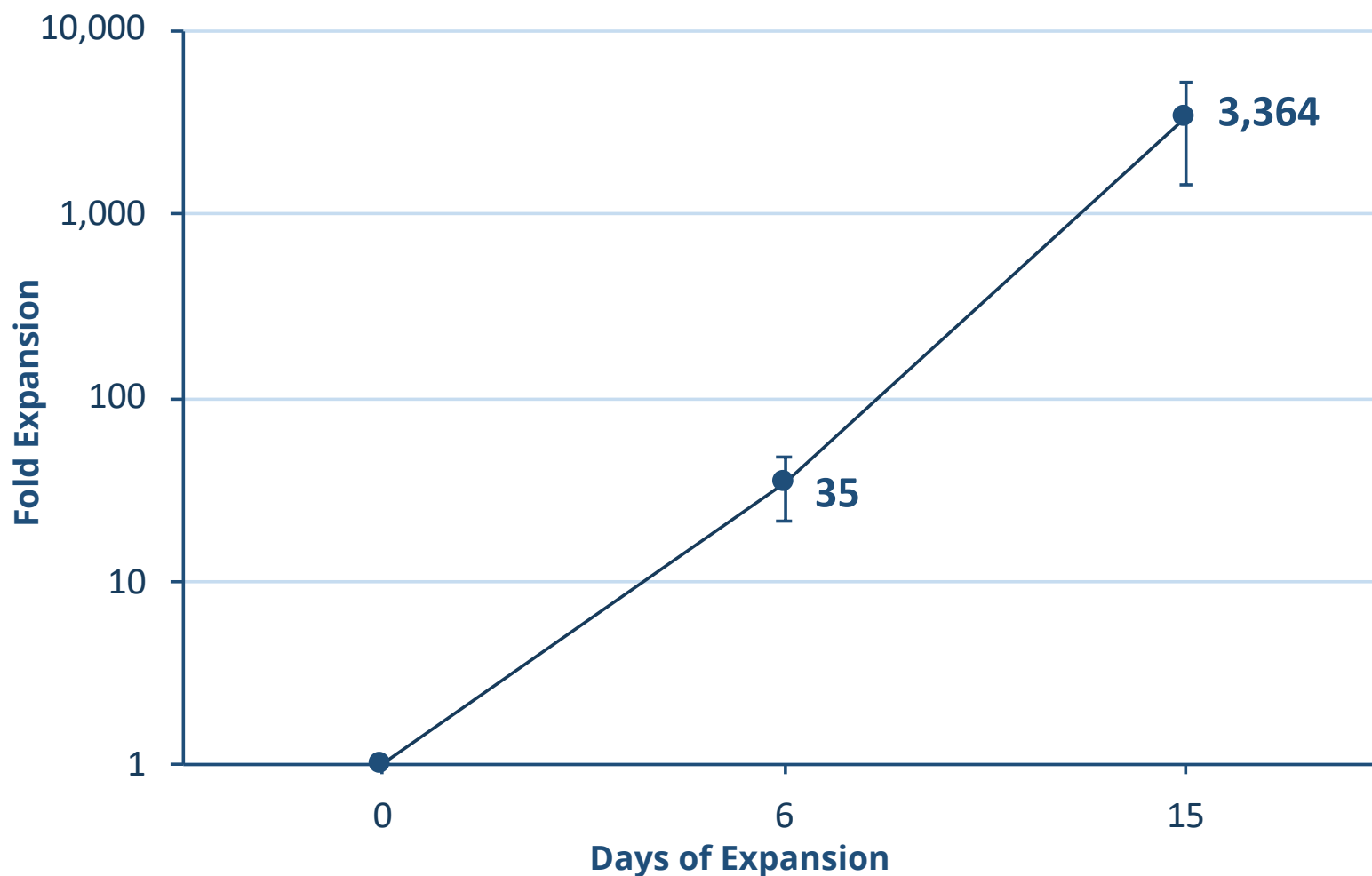
# Manufacturing



# A powerful and efficient process for off-the-shelf products



# Proprietary expansion enables industrial-scale manufacturing



Robust, rapid expansion produces

**≥500** doses

in a single manufacturing run,  
with potential of

**1,000s** of doses  
per run

Projected cost of commercial  
manufacturing at peak:

**~\$2,000**  
per dose\*



## In-house manufacturing to control process and production

### CLINICAL GMP FACILITY

Multi-product facility

Support early clinical trials and research

Manufacturing NKX019 for Phase 1 clinical trial

### FUTURE COMMERCIAL-SCALE FACILITY

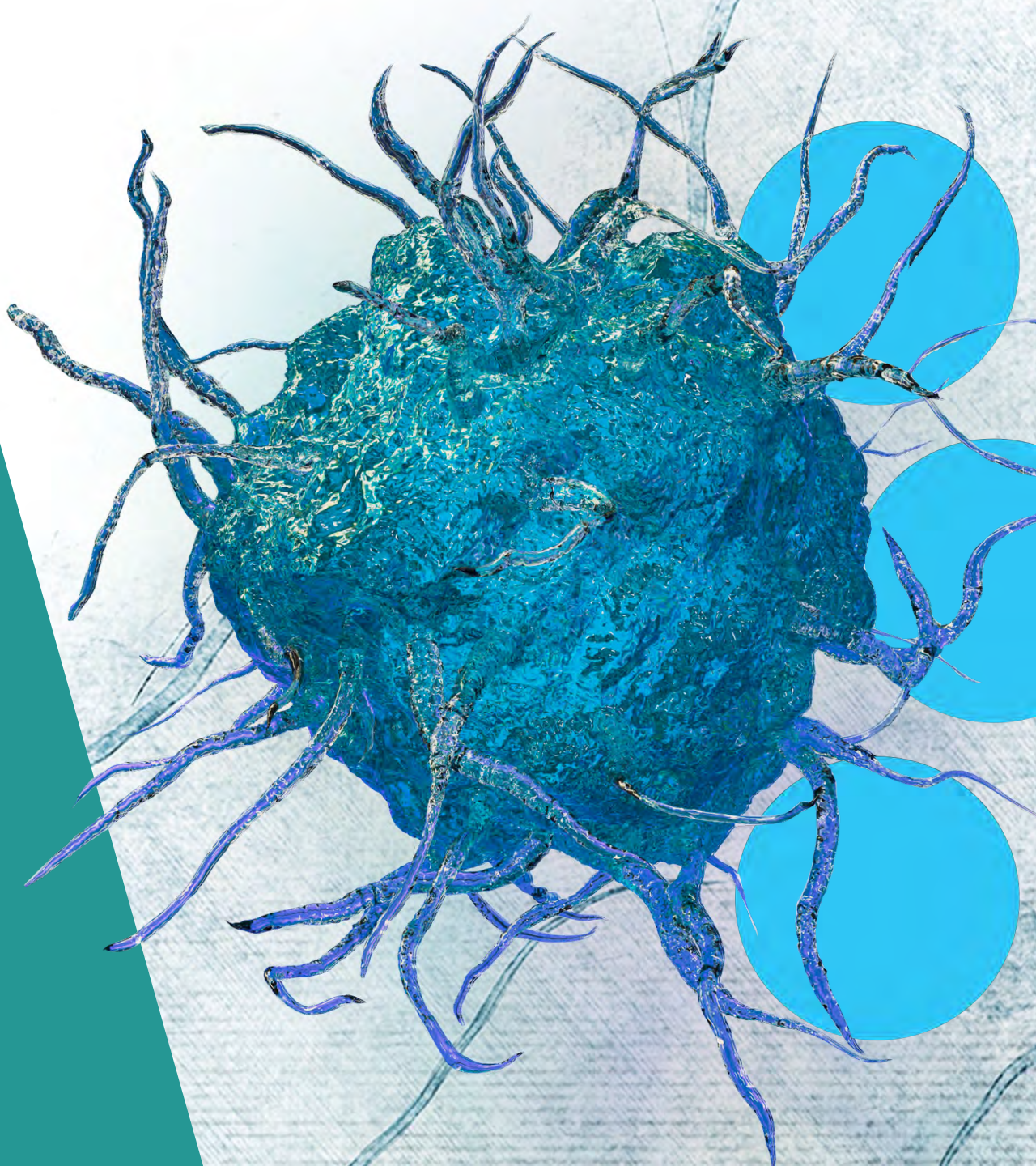
88,000 sq ft facility in South San Francisco

Combined manufacturing hub and company headquarters

Expected to supply pivotal trials and early commercial

Design and engineering process initiated

# Pipeline



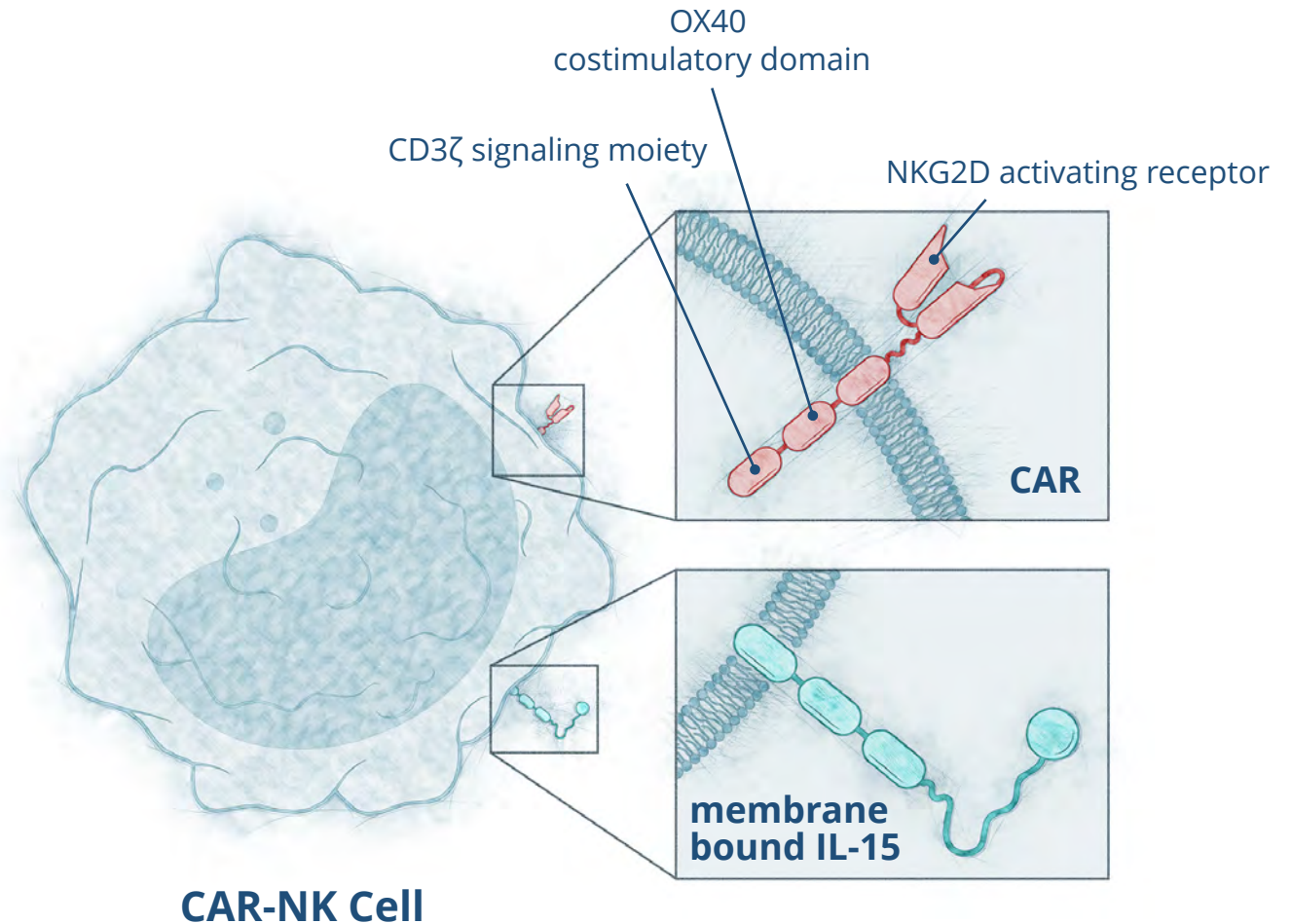
# NKX101: CAR-NK targeting NKG2D ligands

NKG2D receptor is primary driver of NK cell activation and tumor killing

>10x increase in NKG2D expression vs. non-engineered NK cells

OX40 selected based on superiority vs. other costimulatory domains

Targets of NKG2D are selectively over-expressed in cancer cells



# NKG2D: ligands in multiple tumors, responses in AML

## NKG2D ligand expression in multiple tumor types

TUMOR TYPE	REFERENCE
AML, ALL, CML, CLL	<a href="#">Hilpert, J Immunol 2012</a>
MULTIPLE MYELOMA	<a href="#">Carbone, Blood 2005</a>
HCC	<a href="#">Kamimura, J Hep 2012</a>
BREAST	<a href="#">de Kruijf, BMC Can 2012</a>
OVARIAN	<a href="#">McGilvray, Int J Can 2010</a>
LUNG	<a href="#">Okita, Can Imm Immunother 2016</a>
COLON	<a href="#">McGilvray, CCR 2009</a>
MELANOMA	<a href="#">Vetter, J Inv Derm 2002</a>
OSTEOSARCOMA	<a href="#">Lu, Neoplasma 2008</a>
GLIOMA	<a href="#">Weiss, CCR 2018</a>

## Clinical responses observed in r/r AML

- Non-engineered allogeneic NK cells
- Heterogeneous patient population
- Single center academic studies
- 19% true CR rate (aggregate)

STUDY	Response
<a href="#">Bachanova, Crit Rev Oncog 2014, A+B cohorts</a>	<b>9 / 42 (21%)</b>
<a href="#">Bachanova, Crit Rev Oncog 2014, C cohort</a>	<b>8 / 15 (53%)</b>
<a href="#">Curti, Blood 2011</a>	<b>1 / 5 (20%)</b>
<a href="#">Kottaridis, PLOS One 2015</a>	<b>1 / 1 (100%)</b>
<a href="#">Miller, Blood 2005</a>	<b>5 / 19 (26%)</b>
<a href="#">Romee, Sci Transl Med 2016</a>	<b>5 / 9 (56%)</b>
<a href="#">Rubnitz, Pediatr Blood Cancer 2015</a>	<b>6 / 12 (50%)</b>
<b>OVERALL</b>	<b>35 / 103 (34%)*</b>

\*AML responses in patients with morphologic disease at baseline as reported in individual trials, patients with CR at study entry excluded from summary. The 35 responses include 20 CR, 12 CRi, 2 CRp and 1 MLFS.

# NKX101: Rationale in acute myeloid leukemia (AML)

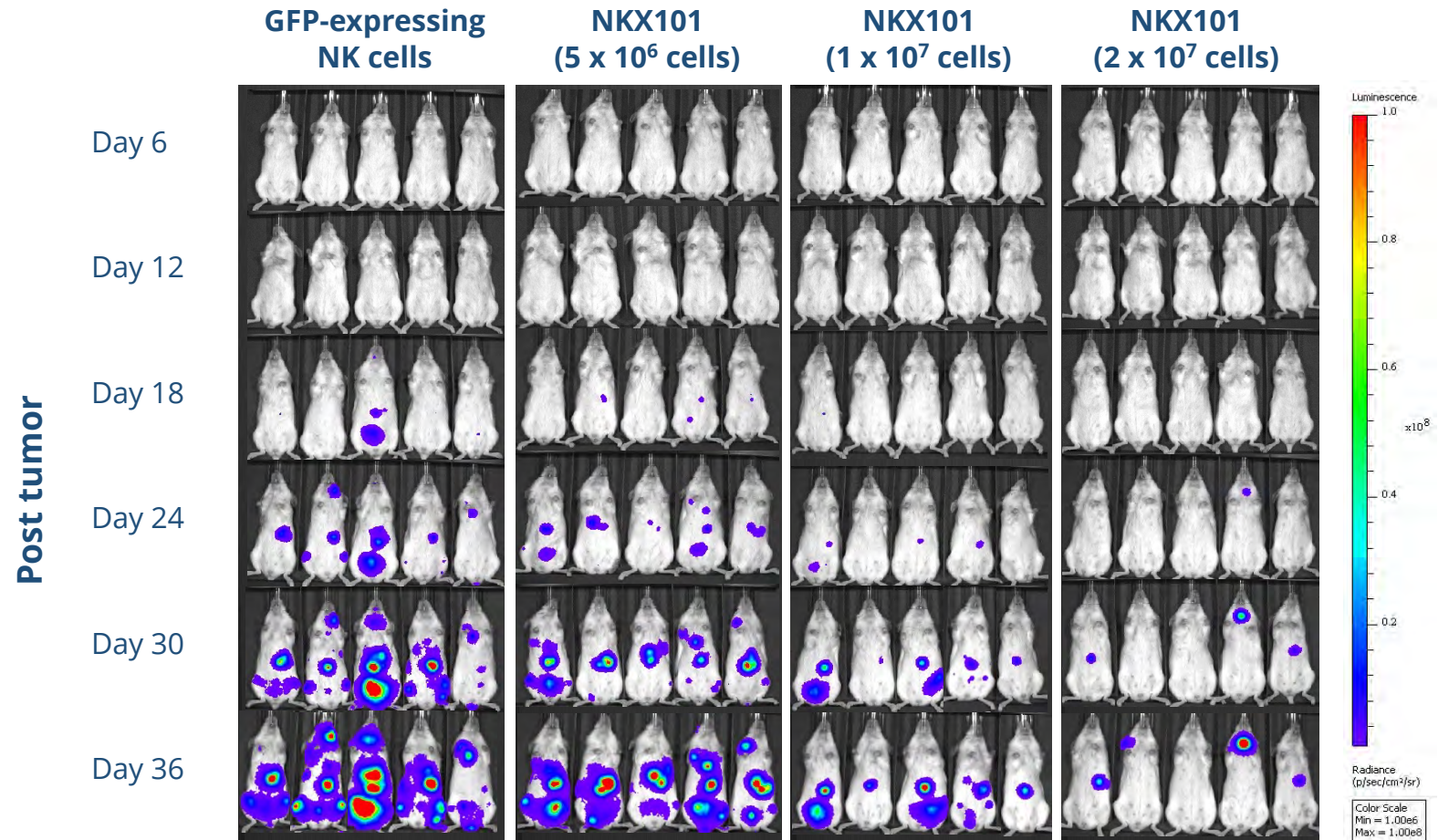
**NKG2D TARGETS  
ARE OVER-EXPRESSED**  
in AML blasts

**CLINICAL ACTIVITY**  
with non-engineered NKs

## UNMET NEED:

- AML US incidence: ~21K / yr
- No approved therapy for patients with r/r AML
- 12 to 18% CR rate in r/r AML population with recycle chemotherapy

Sources: SEER database; Veluchamy, *Front Immunol* 2017; Brayer ASH 2018; Hilpert, *J Immunol*, 2012; Roboz et al, *JCO* 2014; Faderl et al, *JCO* 2012; Ravandi et al, *Lancet* 2015.



THP-1 xenograft model treated with a single dose of NK cells (i.v.)  
2 days after tumor injection

# NKX101 Trial Design

- Multi-cycle
- Multi-dosing per cycle
  - Same cumulative dose, regardless of regimen
  - Regimen A: 3 doses/cycle
  - Regimen B: 2 doses/cycle
- 3 dose levels
  - 300 M, 900 M or 3 B TOTAL CAR-NK cells per cycle
- Modified 3+3 design

## Single-arm two-part multi-center Phase 1 study evaluating safety and efficacy of NKX101 in r/r AML and higher-risk MDS patients



Up to 5 treatment cycles  
with FDA concurrence

[NCT04623944](#)

AML: acute myeloid leukemia  
MDS: myelodysplastic syndrome

# NKX101 demonstrates anti-tumor activity in solid tumors

**LIVER & BILE CANCER US  
INCIDENCE: ~42K / YR**

5-year survival rate ~18%

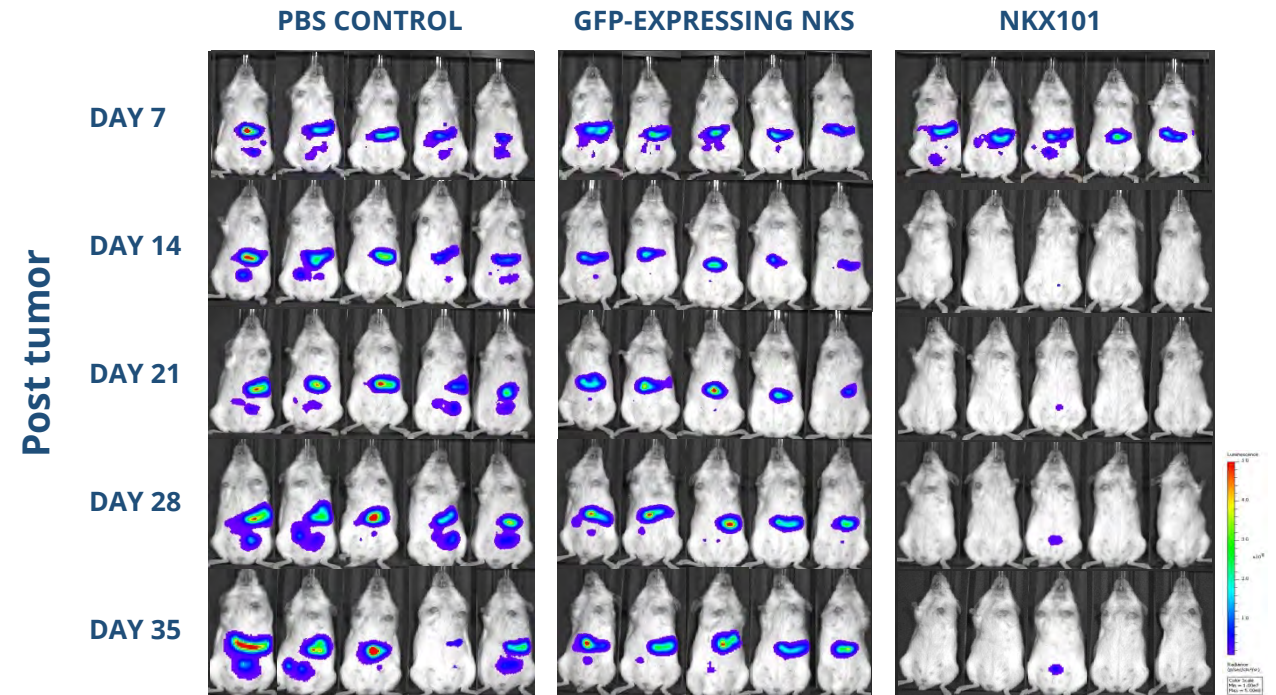
**NKG2D TARGETS OVER-EXPRESSED**  
on HCC and CRC cells

**NK CELLS ARE IMPORTANT IN LIVER**  
immunity and tumor surveillance

**ACTIVITY OF NON-ENGINEERED NK**  
cells in HCC/ICC: 3/16 PRs

**PLANNED PHASE 1: LOCOREGIONAL**  
delivery using SOC technique in 1° liver  
cancer or liver metastases

## NKX101 activity in NSG mice



SNU449 HCC xenograft model  
3 x 10<sup>6</sup> NK cells injected at day 7 post-tumor

HCC: Hepatocellular carcinoma. CRC: Colorectal cancer. Sources: SEER database; Sun Act Pharm Sin 2015; Kamimura, J Hepatology, 2012; Kamiya et. al, Cancer Immunol Res 2016; Qin 2017

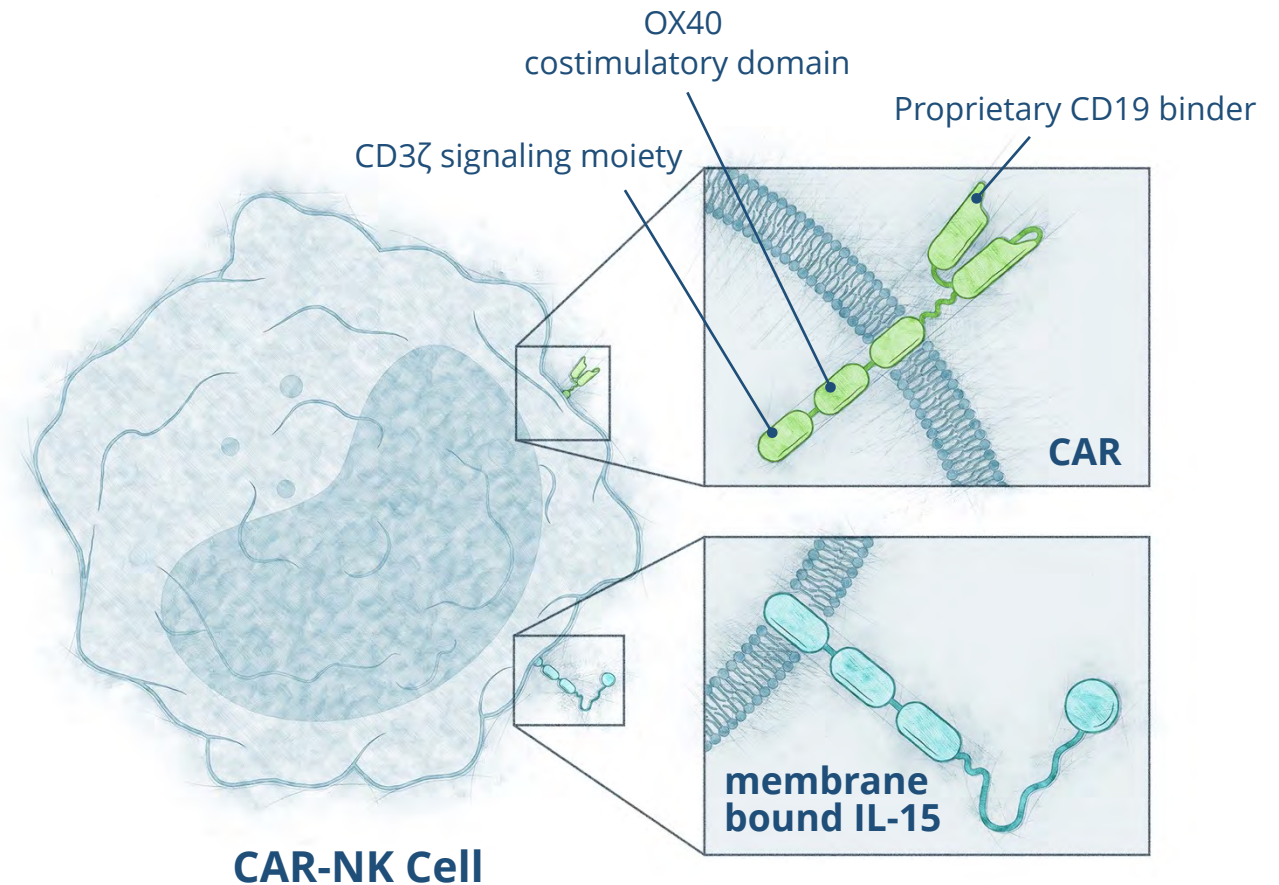
# NKX019: CD19 targeted CAR-NK

## UNMET NEED REMAINS DUE to SAFETY, SPEED, ACCESS of APPROVED CD19 CAR-T THERAPIES

- Gr3+ CRS: 13 to 49%; Gr3+ neurotoxicity: 18 to 31%
- Limited number of specialized sites can treat
- 9 to 34% of patients in pivotal trials did not receive cells (primarily due to mfg. challenges)

## IL-12 and IL-18 EXPANSION ENHANCES *IN VITRO* and *IN VIVO* CYTOTOXICITY and PERSISTENCE

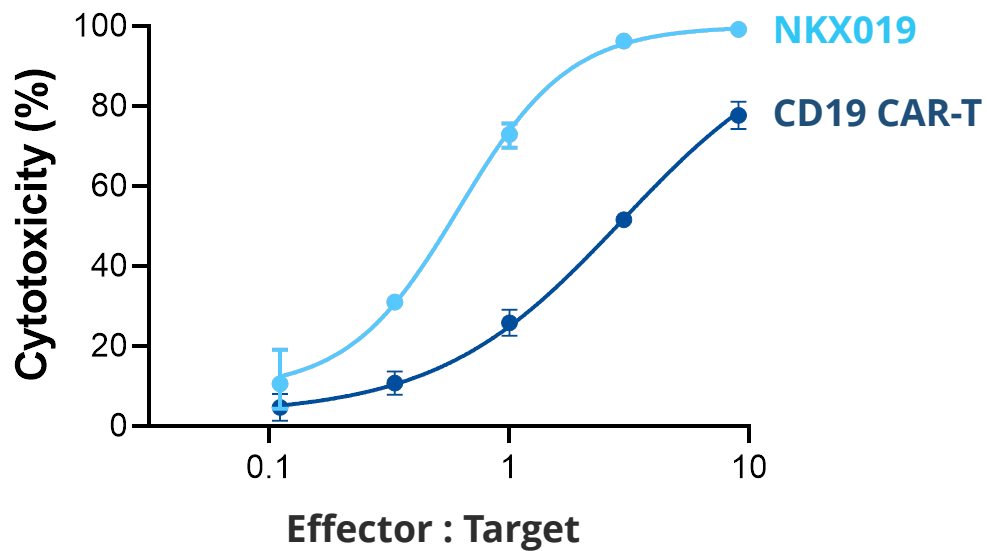
- In combination with Nkarta's NKSTIM feeder NK expansion platform



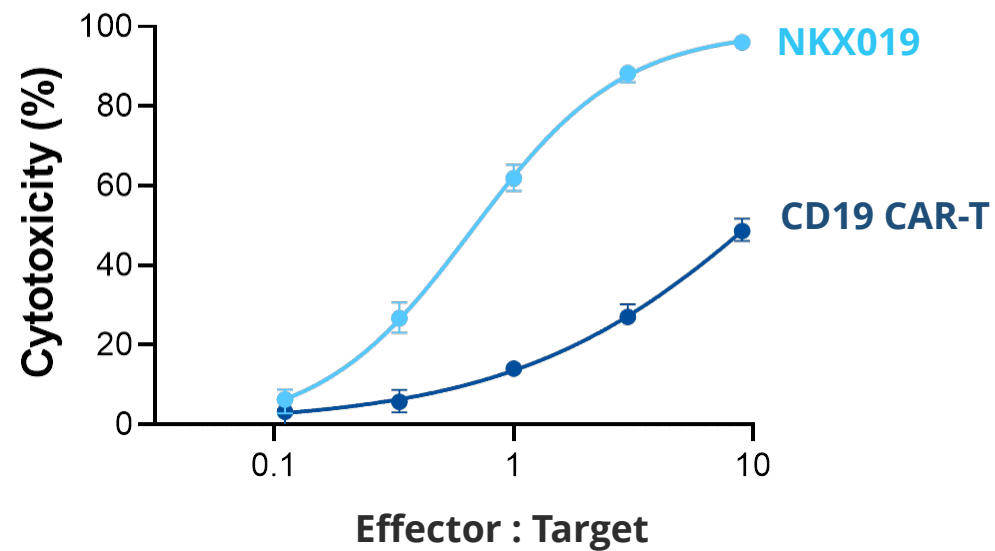
Sources: Kymriah® and Yescarta® package inserts; Rezvani NEJM 2020. Per NEJM publication, CR/SD patient achieved a CR for Richter's transformation and SD for underlying CLL. [Trager SITC 2019.](#)

# NKX019 kills tumors with high or low levels of CD19 expression

## High CD19 Expressing Cells



## Low CD19 Expressing Cells

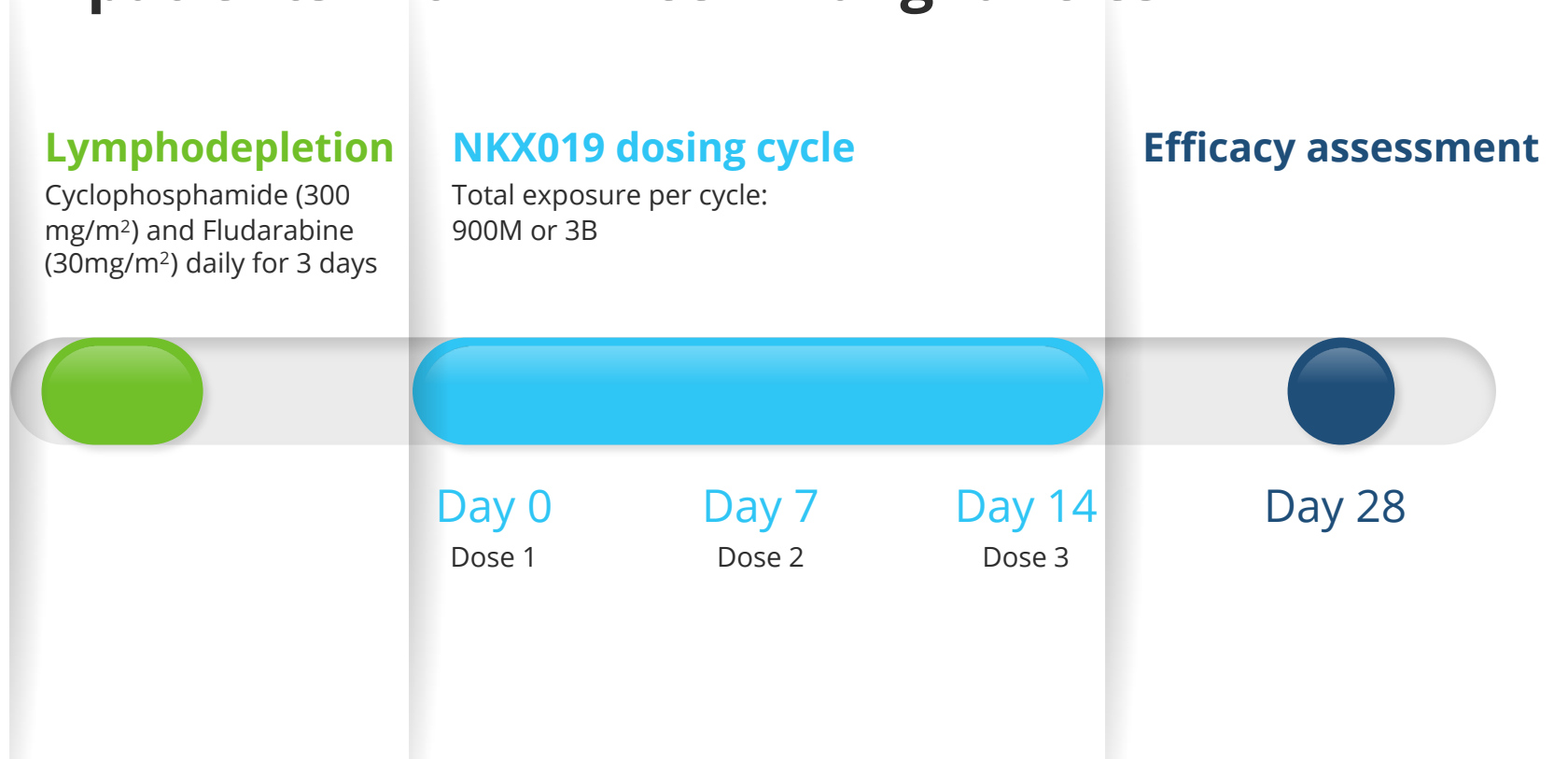


**NKX019 can achieve high levels of cytotoxicity even when tumor cells express low levels of CD19 antigen, whereas CD19-targeted T cells are not as efficacious**

# NKX019 Trial Design

- Multi-cycle
- Multi-dosing per cycle
  - 3 doses per cycle
- 2 dose levels
  - 300 M, 1 B CAR NK cells per dose
- Modified 3+3 design
- Dose finding followed by multiple dose expansion cohorts

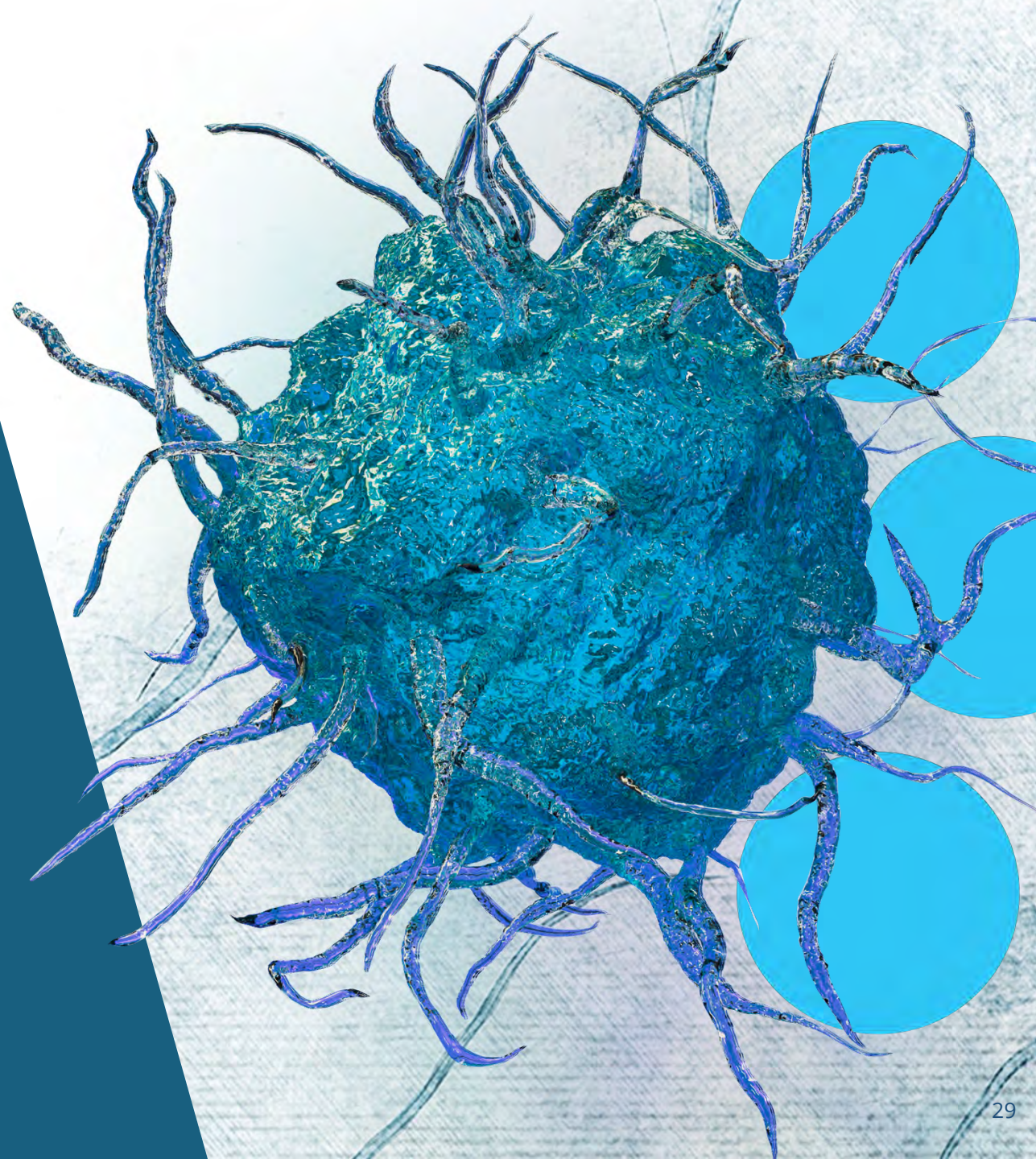
## Single-arm multi-center Phase 1 study evaluating safety and efficacy of NKX019 in patients with r/r B cell malignancies



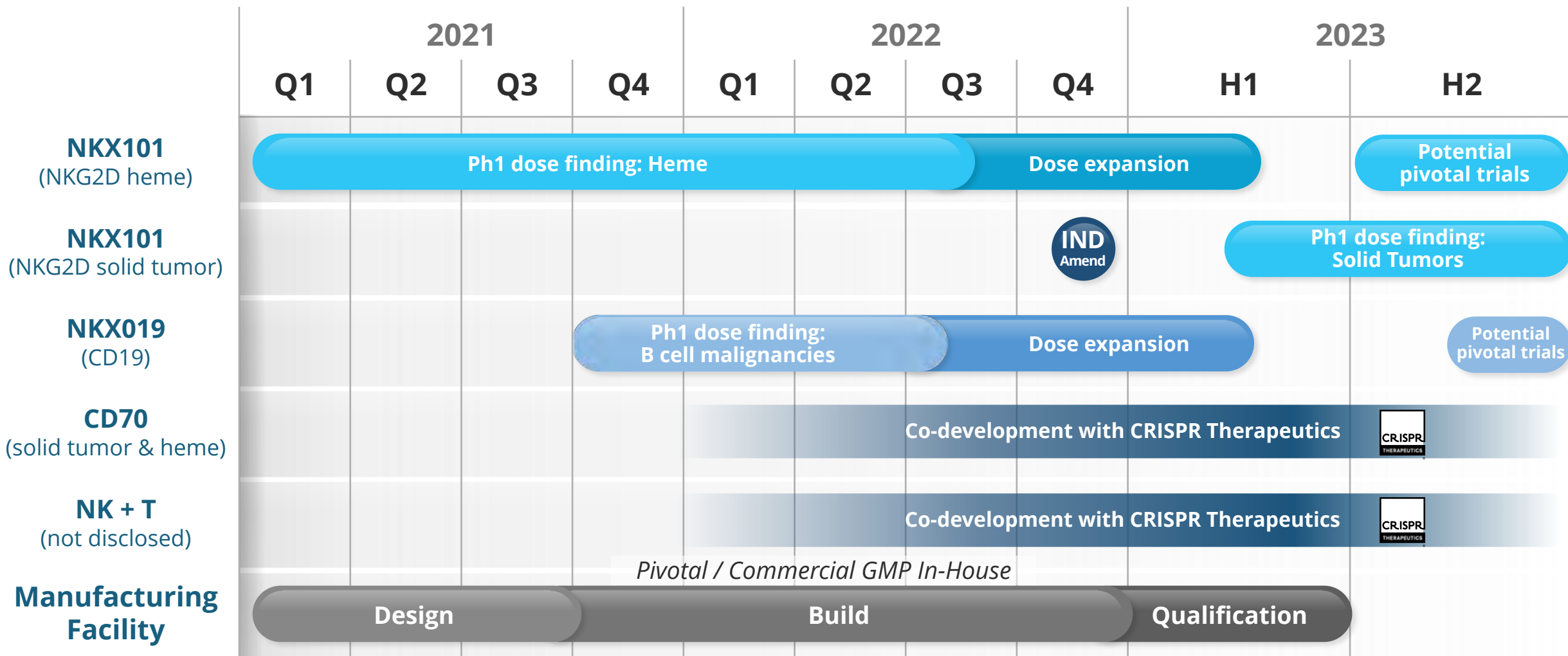
[NCT05020678](#)

Up to 5 treatment cycles

# Corporate



# Platform-driven pipeline with multiple upcoming milestones



# Our Vision and Mission

## OUR VISION

*To be the leading company delivering innovative, accessible cell therapies for cancer patients, their caregivers and families*

## OUR MISSION

*We strive to discover, develop and deliver novel off-the-shelf NK cell therapy product candidates that have a profound impact on cancer patients*

Thank you!

